

# Hepatitis in the HIV Infected Adult

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**UTMB-Correctional Managed Care**

# Speaker Disclosure of Financial Relationship

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- Dr. Jessica Khan:
  - ❖ Will disclose to the audience if she will be discussing any unlabeled or investigational use of commercial products
  - ❖ Does not now, or in the last 12 months, have a relevant financial relationship with a commercial interest; nor does her spouse

# Course Objectives

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- Describe epidemiology of Viral Hepatitides in HIV patients
- Describe the course of viral hepatitides in HIV infected patients and compare and contrast them with those not infected with HIV
- Discuss disease management and current treatment options for the co-infected patient including toxicity management
- Summarize data on future management trends for viral hepatitides.



# Hepatitis A

Picornavirus family  
(genus Hepatovirus)

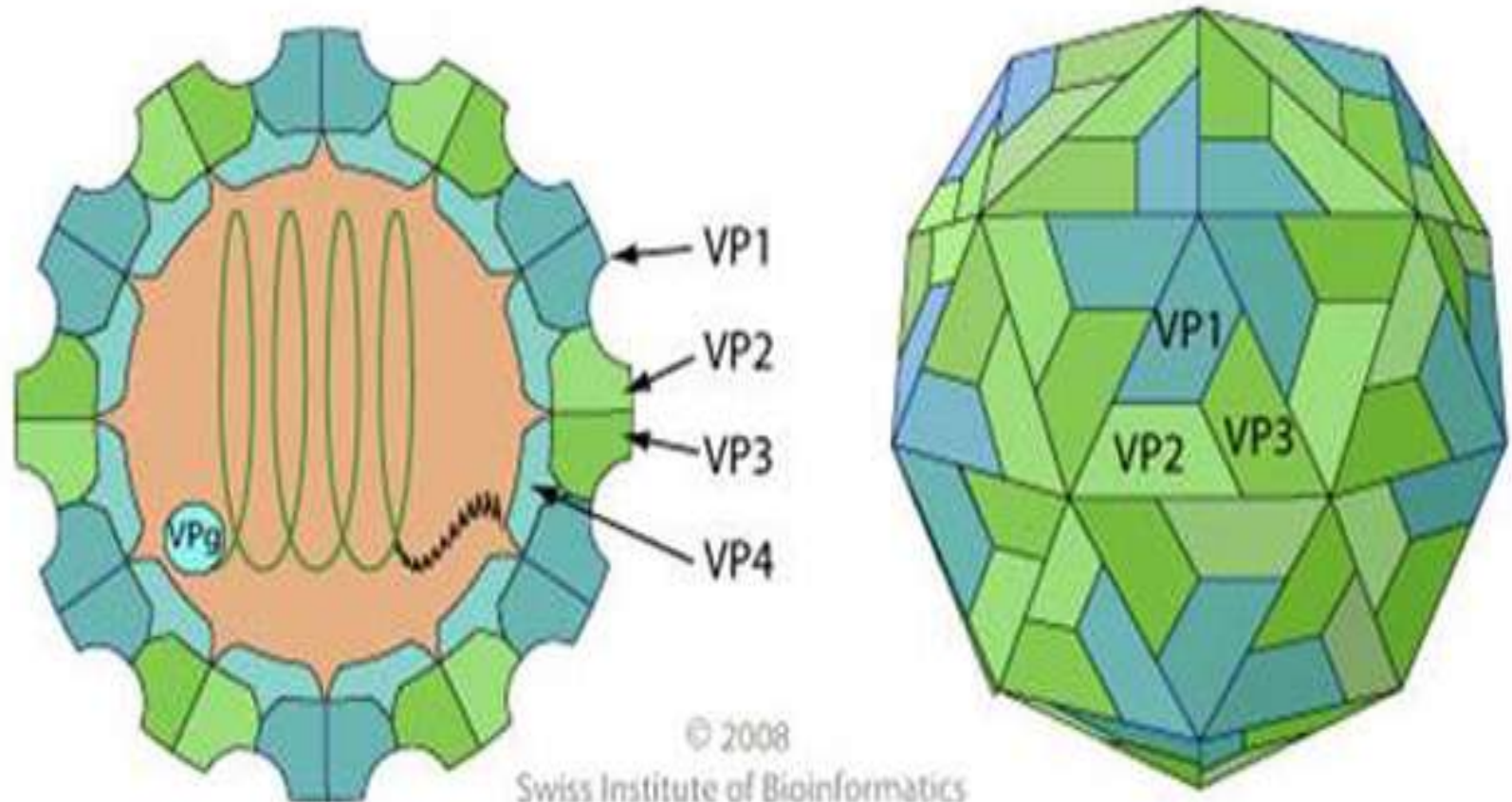
Nonenveloped; ssRNA  
27-32 nm in diameter

One human serotype

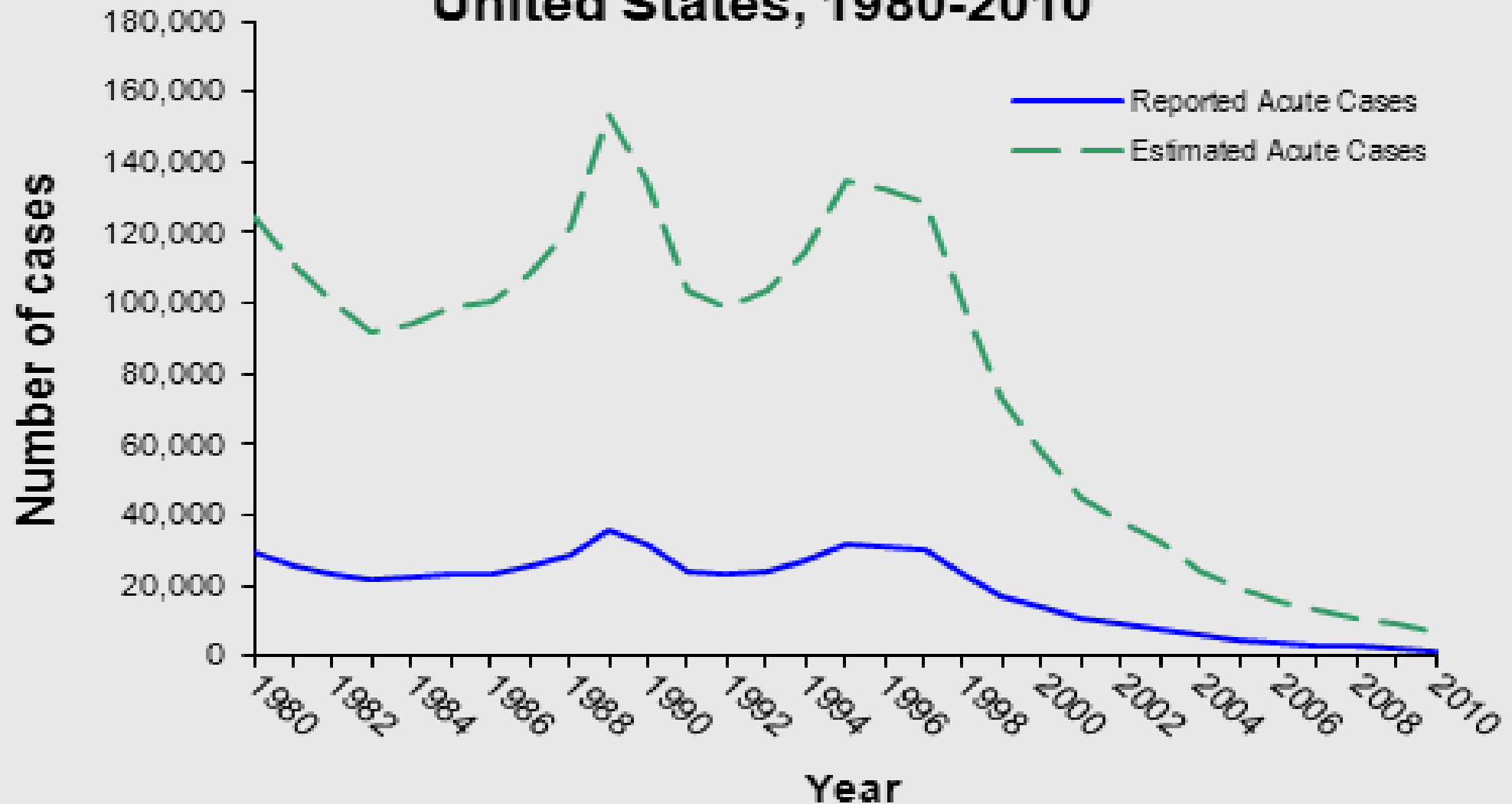
Replicates in the liver

Shed in high levels in  
feces from 2 wks  
before and 1 wk after  
symptoms

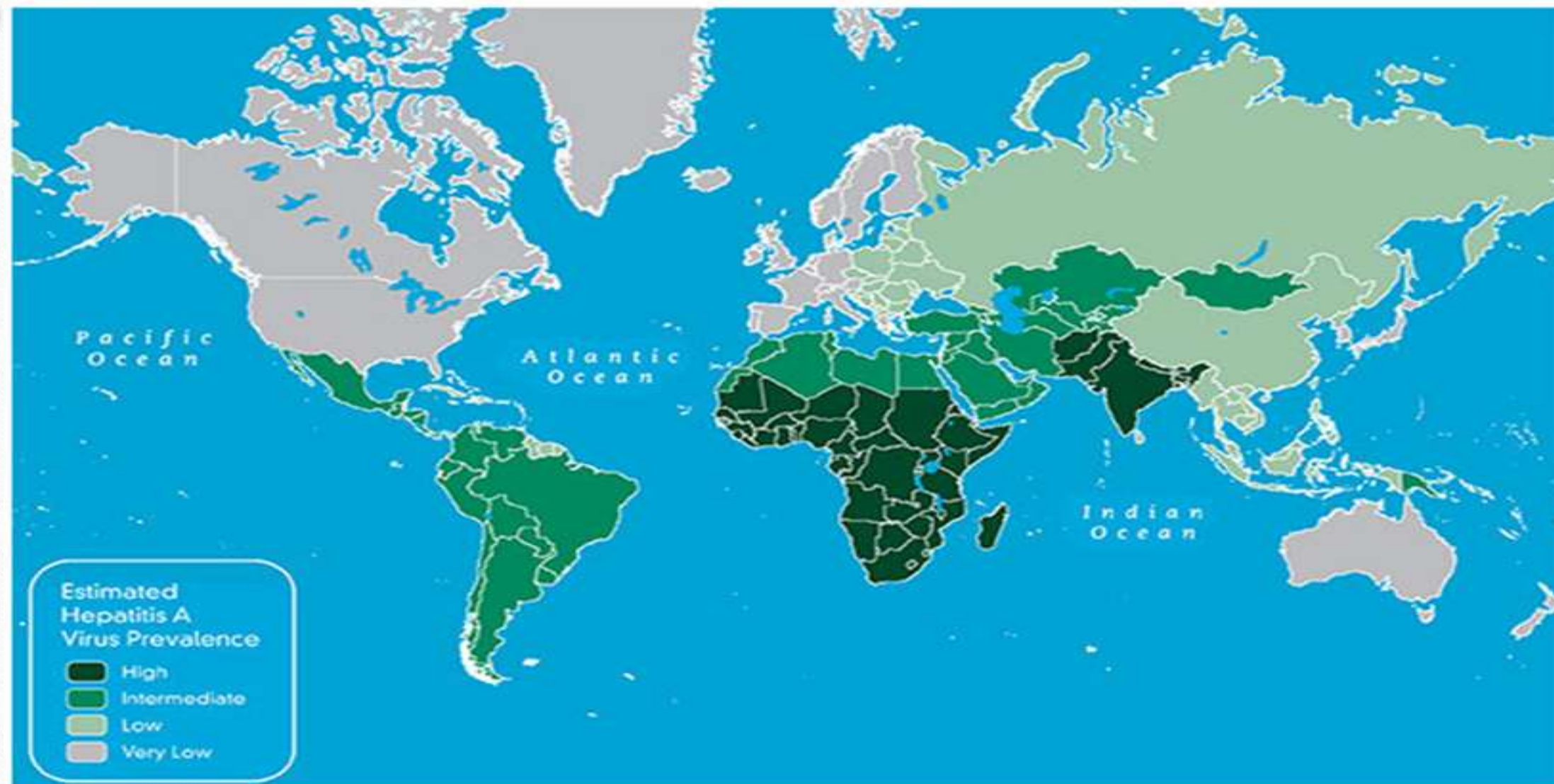
## Hepatitis A



## Incidence of Hepatitis A, by year United States, 1980-2010



Map 3-03. Estimated prevalence of hepatitis A virus<sup>1,2</sup>



<sup>1</sup>Jacobsen KH, Wiersma ST. Hepatitis A virus seroprevalence by age and world region, 1990 and 2005. *Vaccine*. 2010 Sep 24;28(41):6653-7. Data used with permission from Elsevier.

## **Factors that increases risk for acquiring HAV**

- Travelers to countries with moderate to high endemicity of HAV
- Men who have sex with men
- Users of injection and non-injection illegal drugs
- Persons with clotting factor disorders
- Persons working with nonhuman primates

# Hepatitis A Facts

- Mode of transmission  
fecal to oral
- Incubation period  
average 30 days  
range 15-50 days
- Chronic form of disease  
none
- Duration of symptoms  
usually less than 2 months
- Survival outside the body  
months in the right conditions;  
killed by heating 185° F X 1 min

# Acute hepatitis

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discrete onset of symptoms

nausea

anorexia

fever

malaise

abdominal pain

dark urine

clay colored stool

jaundice

elevated transaminases

\*confirm with HAV IgM &/or Hx  
of exposure to HAV active contact  
within the correct time period

# HIV/HAV CO-INFECTION

- Usually not more severe but can be more aggressive in HIV+ patients
- 
- Can be severe in chronic liver disease patients
  - Studies have shown that HIV infected patients had a prolonged duration of viral shedding
  - Acute infection may cause temporary interruption in ART therapy (implications on transmission in the community)

# Diagnosis of Hepatitis A

TEST	INTERPRETATION
IGM ANTI-HAV	ACTIVE OR RECENT HAV INFECTION
IGG ANTI-HAV (TOTAL ANTI-HAV)	CURRENT OR PAST HAV INFECTION; PREVIOUSLY VACCINATED

# HAV Treatment

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- Supportive care
  - No restrictions on diet or activity
- Hospitalization for dehydration (N/V/D)
- Liver toxic medications should be used with caution during acute HAV and acute liver injury

# Hepatitis A

## Licensed Hepatitis A Vaccines

Vaccine	Age	Dose	Volume	# Doses	Schedule
VAQTA	1-18 years	25 Units	0.5 ml	2	0, 6-18 mos
	≥ 19 years	50 Units	1.0 ml	2	0, 6-18 mos
HAVRIX	1-18 years	720 ELISA Units	0.5 ml	2	0, 6-12 mos
	≥ 19 years	1440 ELISA Units	1.0 ml	2	0, 6-12 mos
TWINRIX*	≥ 18 years	720 ELISA Units 20 ug	0.5 ml	3	0, 1, 6 mos

# Who should be vaccinated against Hepatitis A?

***All children at age 1 year (i.e., 12–23 months).***

***Children and adolescents ages 2–18 who live in states or communities where routine Hepatitis A vaccination has been implemented because of high disease incidence.***

***Persons traveling to or working in countries that have high or intermediate rates of Hepatitis A.***

***Men who have sex with men.***

***Users of illegal injection and noninjection drugs.***

***Persons who have occupational risk for infection.***

***Persons who have chronic liver disease.***

***Persons who have clotting-factor disorders.***

***Household members and other close personal contacts of adopted children newly arriving from countries with high or intermediate hepatitis A endemicity.***

**Which groups do NOT need routine vaccination against Hepatitis A?**

***Food service workers.***

***Sewage workers.***

***Health care workers***

***Child care center attendees.***

***Residents of institutions for developmentally disabled persons.***

# CDC guidelines for postexposure protection against Hepatitis A

- Single Antigen Vaccine or Immune globulin (IG) at 0.02 ml/kg should be given within 2 weeks after exposure
  - Healthy persons aged 12 months-40 years
    - single-antigen Hepatitis A vaccine at the age-appropriate dose.
  - Persons aged >40 years, IG (0.02 ml/kg) is preferred
- Children aged <12 months, immunocompromised persons, persons with chronic liver disease, and persons who are allergic to the vaccine or a vaccine component, IG should be used.



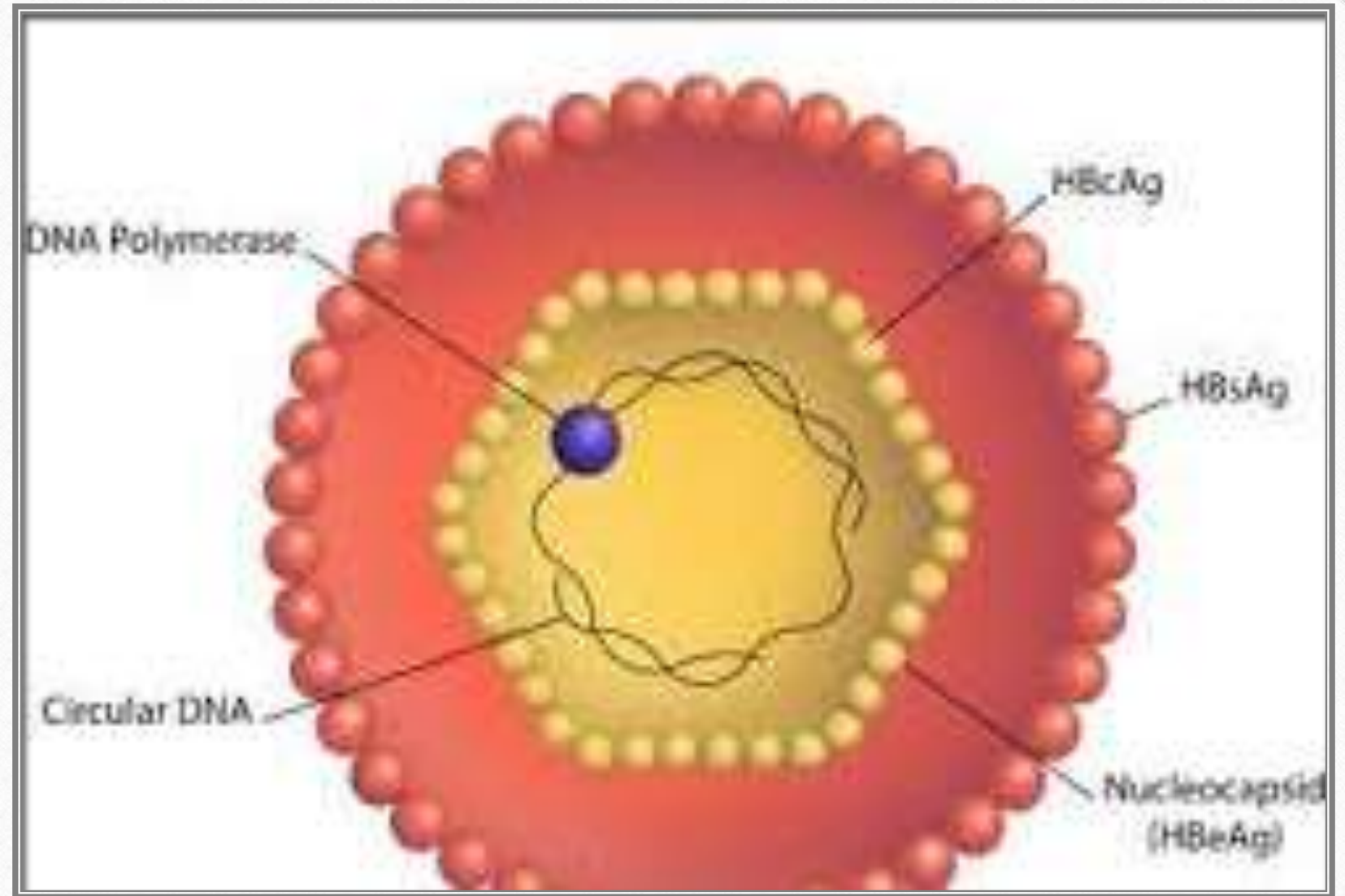
# HEP B in the HIVE

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The Who, When, What and How of  
Treating Hepatitis B Infection

# Hepatitis B the virus

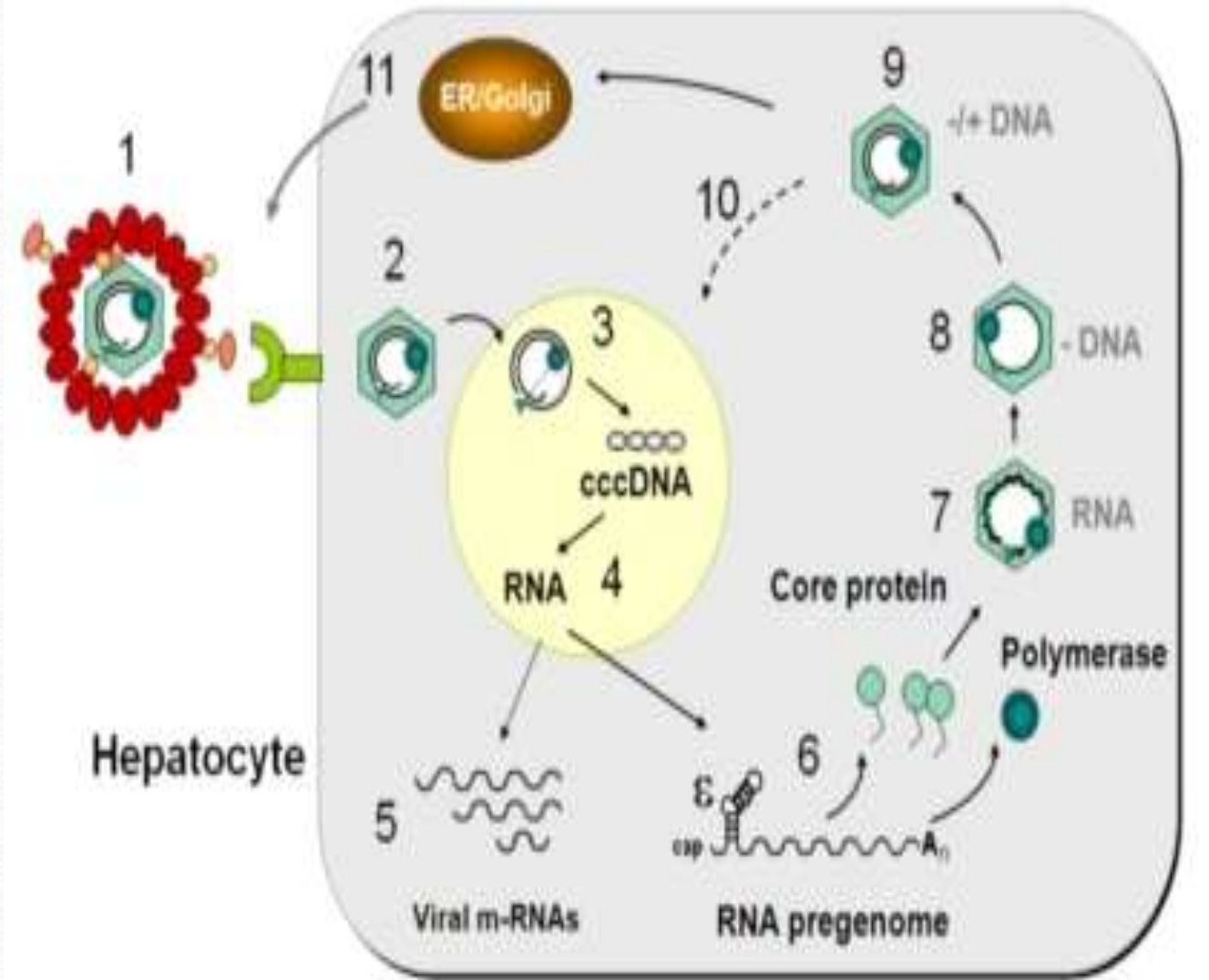
- Hepadnavirus
- Partially double stranded DNA
  - RNA dependent reproduction using reverse transcriptase



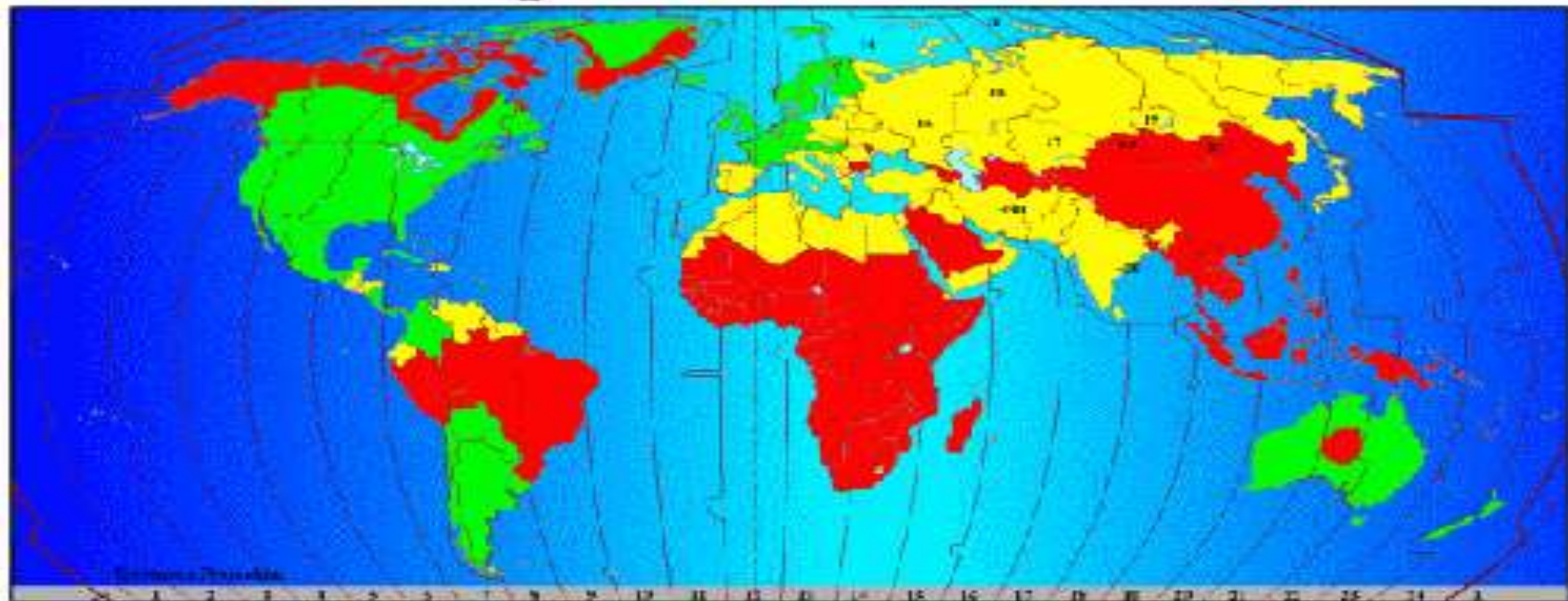
# Hepatitis B the virus

## The HBV life cycle: basis for persistent infection

*Adapted from PD Dr Ulla Schultz,  
University of Freiburg i. Br*



# Global Distribution of Chronic Hepatitis B Infection



■ >8% - High

■ 2% - 7%

■ <2% - Low

Intermediate

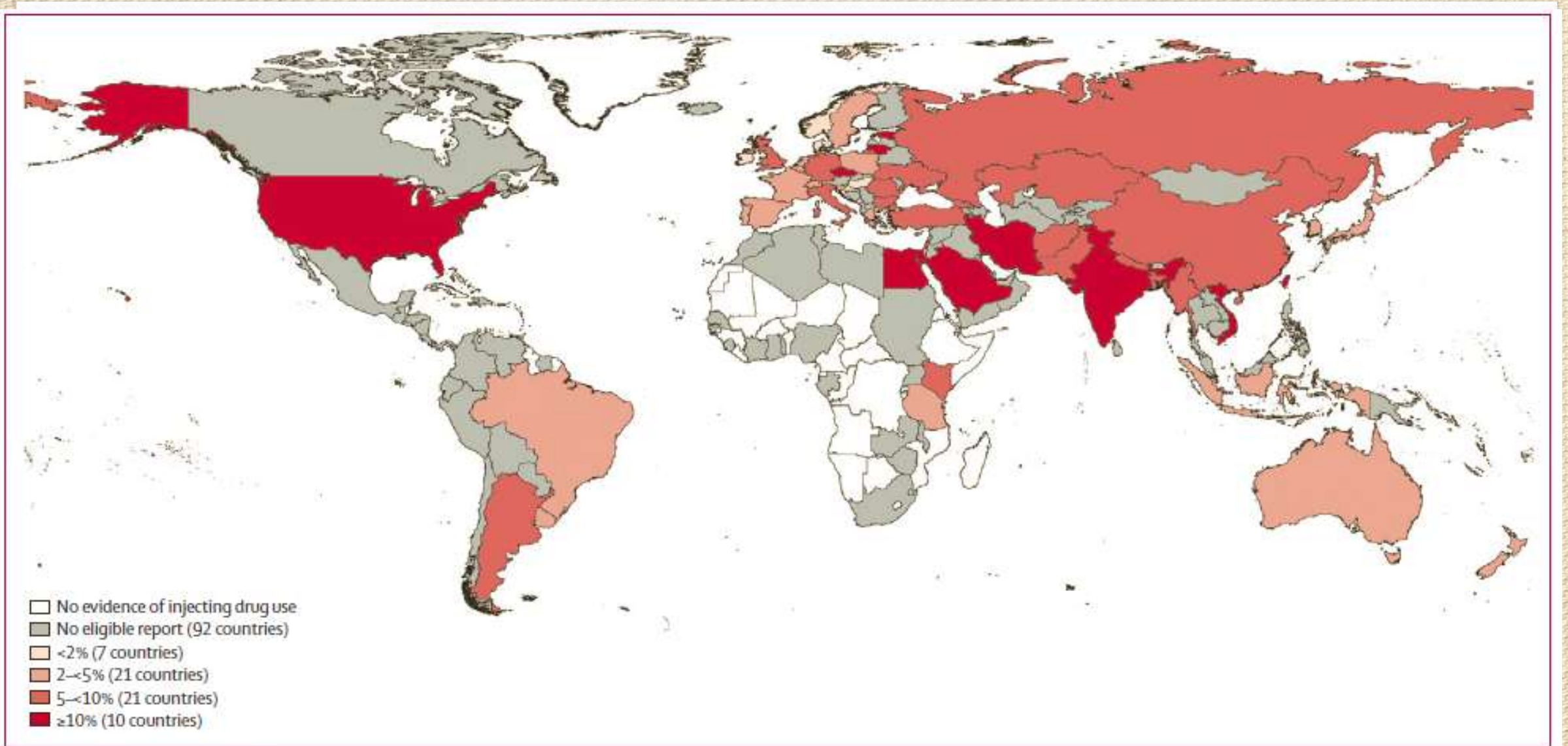
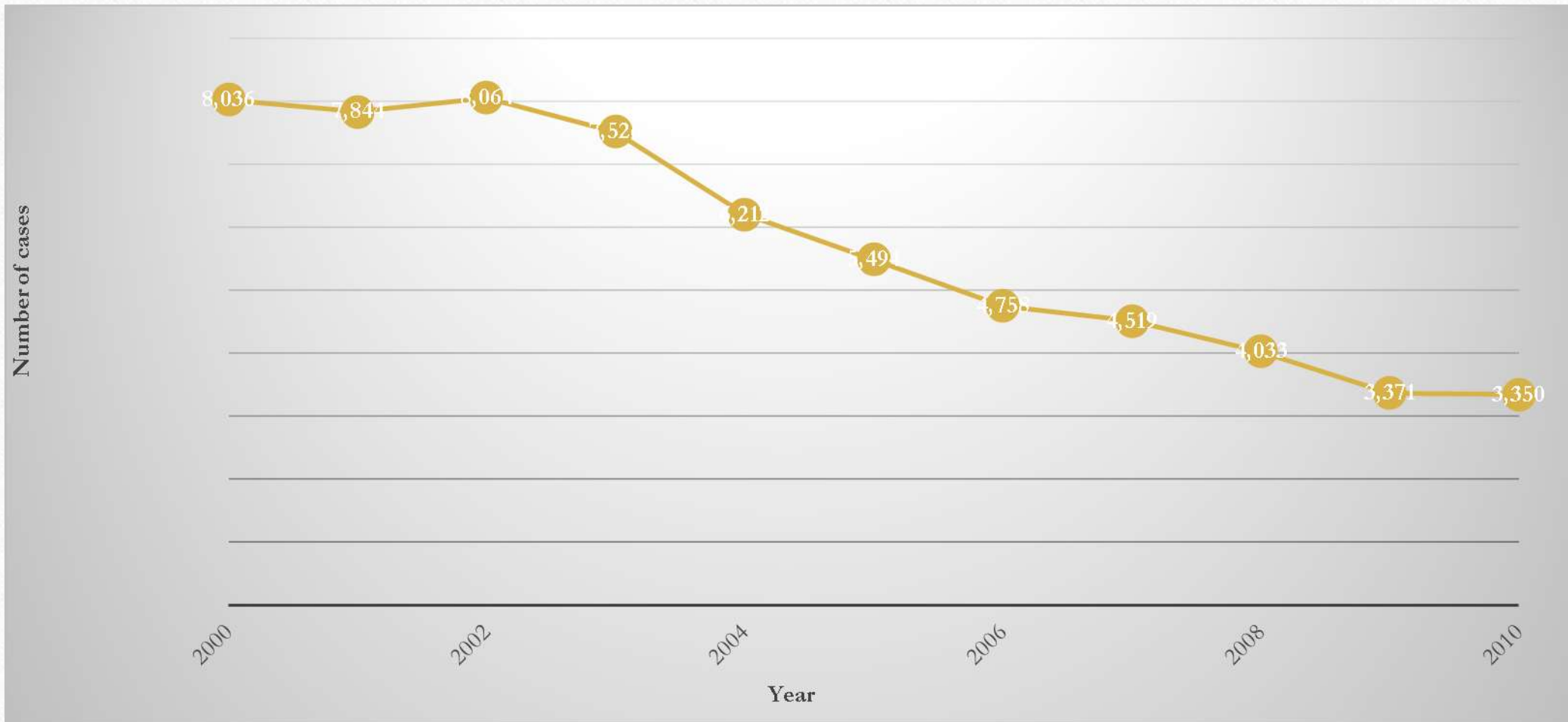


Figure 3: Prevalence of hepatitis B surface antigen in injecting drug users

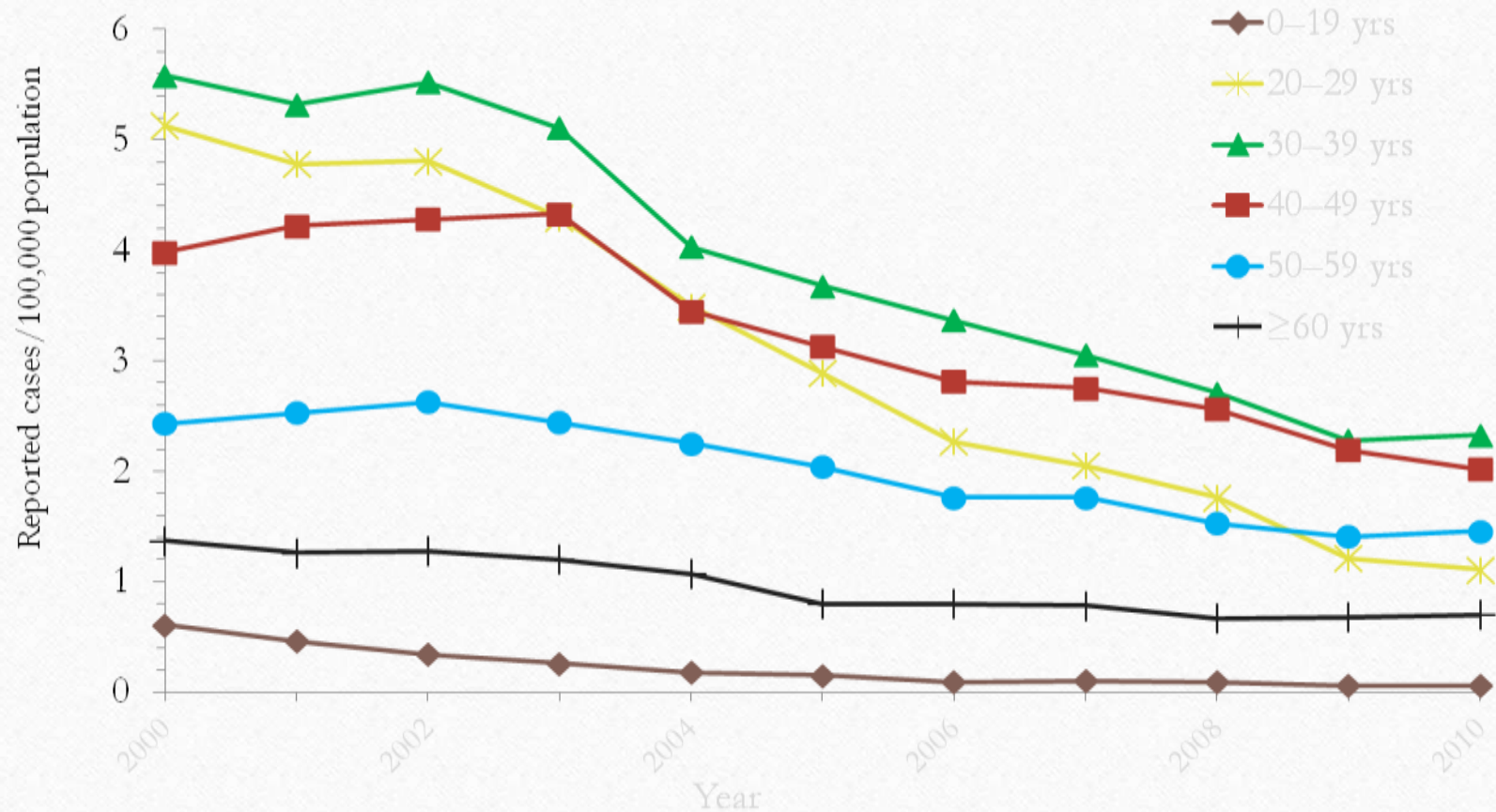
**Figure 3.1. Reported number of acute hepatitis B cases — United States, 2000–2010**



\*Adjusted for underreporting.

Source: National Notifiable Diseases Surveillance System (NNDSS)

**Figure 3.2. Incidence of acute hepatitis B, by age group — United States, 2000–2010**



Source: National Notifiable Diseases Surveillance System (NNDSS)

# Hepatitis B facts

Modes of transmission

parenteral, perinatal, sexual

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Incubation period

3 - 12 weeks

Chronic infection

<5 years --- 30 – 90 %

≥ 5 years --- 2 – 10 %

Premature mortality from ESLD

15 – 25 %

Survival outside the body

only in body fluids:

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High – blood, serum, wound exudate

Moderate – semen, vaginal fluid, saliva

Low/nill – urine, feces, sweat, tears,  
breast milk

# Risk factors for HBV disease

- Have sexual contact with an infected person
  - Have multiple sex partners
- 
- Have a sexually transmitted disease
  - Are men who have sexual encounters with other men
  - Inject drugs or share needles, syringes, or other injection equipment
  - Live with a person who has Hepatitis B
  - Are on hemodialysis
  - Are exposed to blood on the job
  - Are infants born to infected mothers

# Persons who need to be screened for HBV

- Individuals born in areas of high# and intermediate prevalence rates for HBV including immigrants and adopted children
- Household and sexual contacts of HBsAg-positive persons\*
- Persons who have ever injected drugs\*
- Persons with multiple sexual partners or history of sexually transmitted disease\*
- Men who have sex with men\*
- Inmates of correctional facilities\*
- Individuals with chronically elevated ALT or AST\*
- Individuals infected with HCV or HIV\*
- Patients undergoing renal dialysis\*
- All pregnant women

# Acute hepatitis

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discrete onset of symptoms

nausea

anorexia

fever

malaise

abdominal pain

dark urine

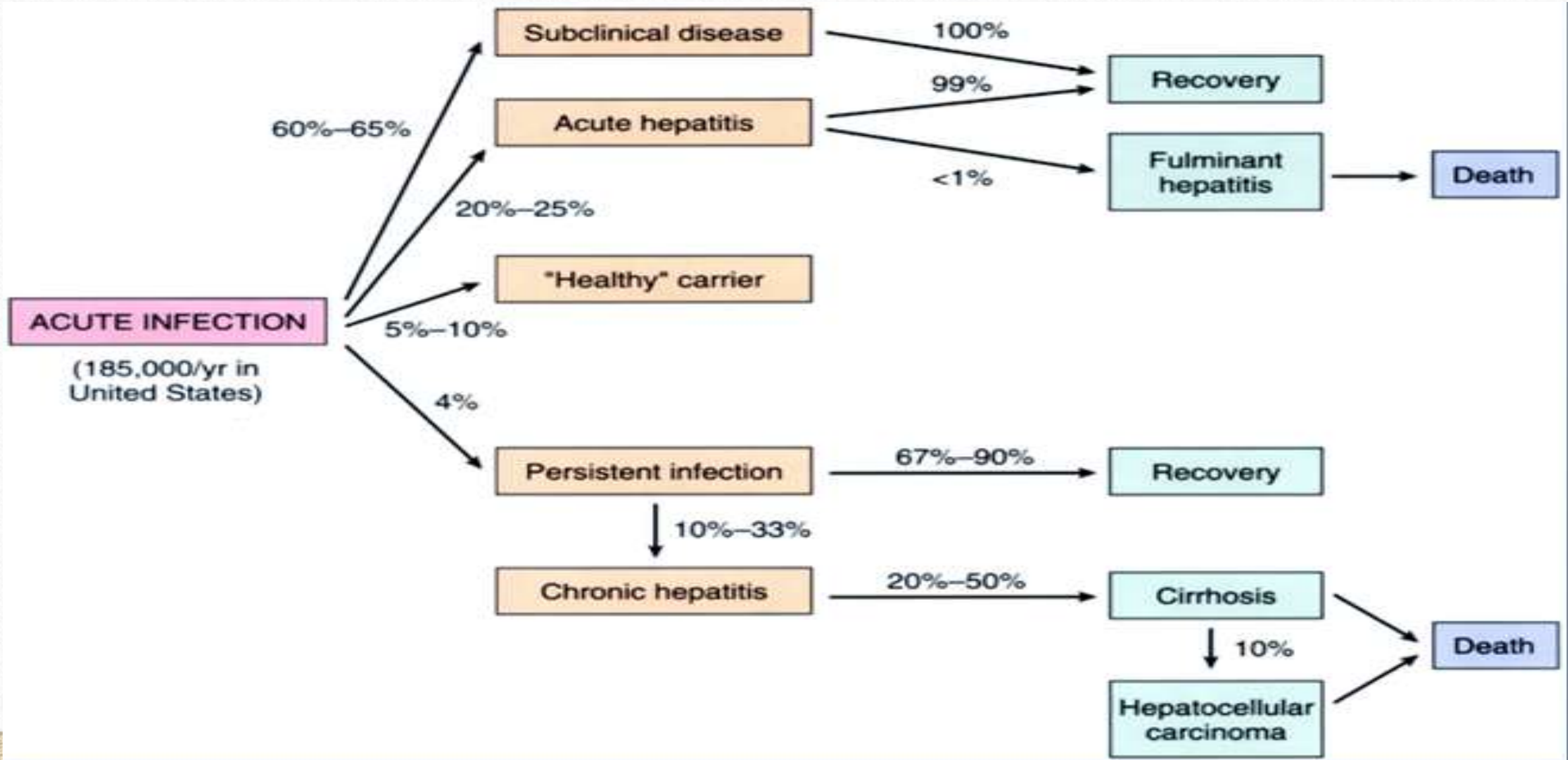
clay colored stool

jaundice

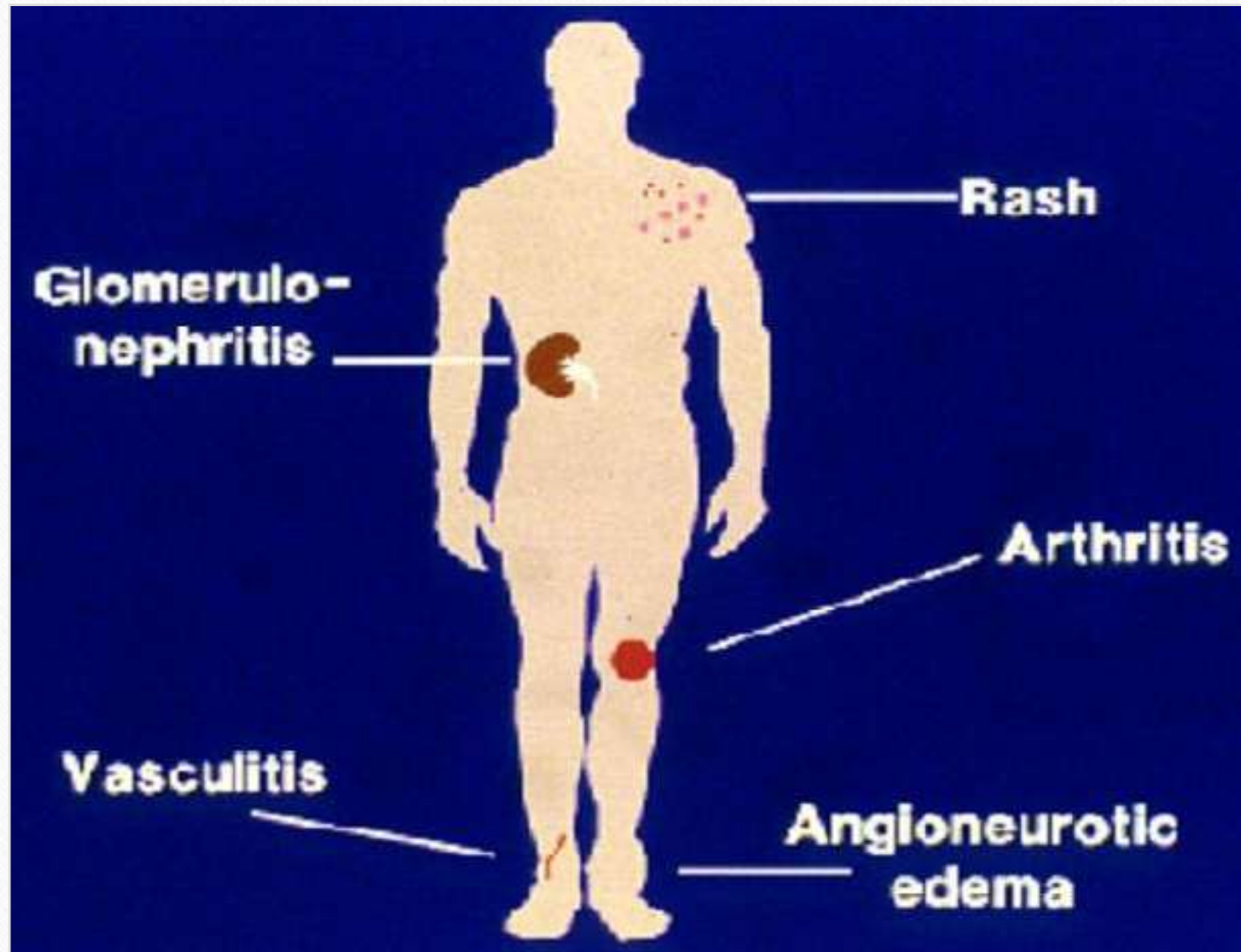
elevated transaminases

**\* confirm with HBcAb IgM &/or Hx  
of exposure to HBV active contact  
within the correct time period**

# Clinical Course of Hepatitis B Infection

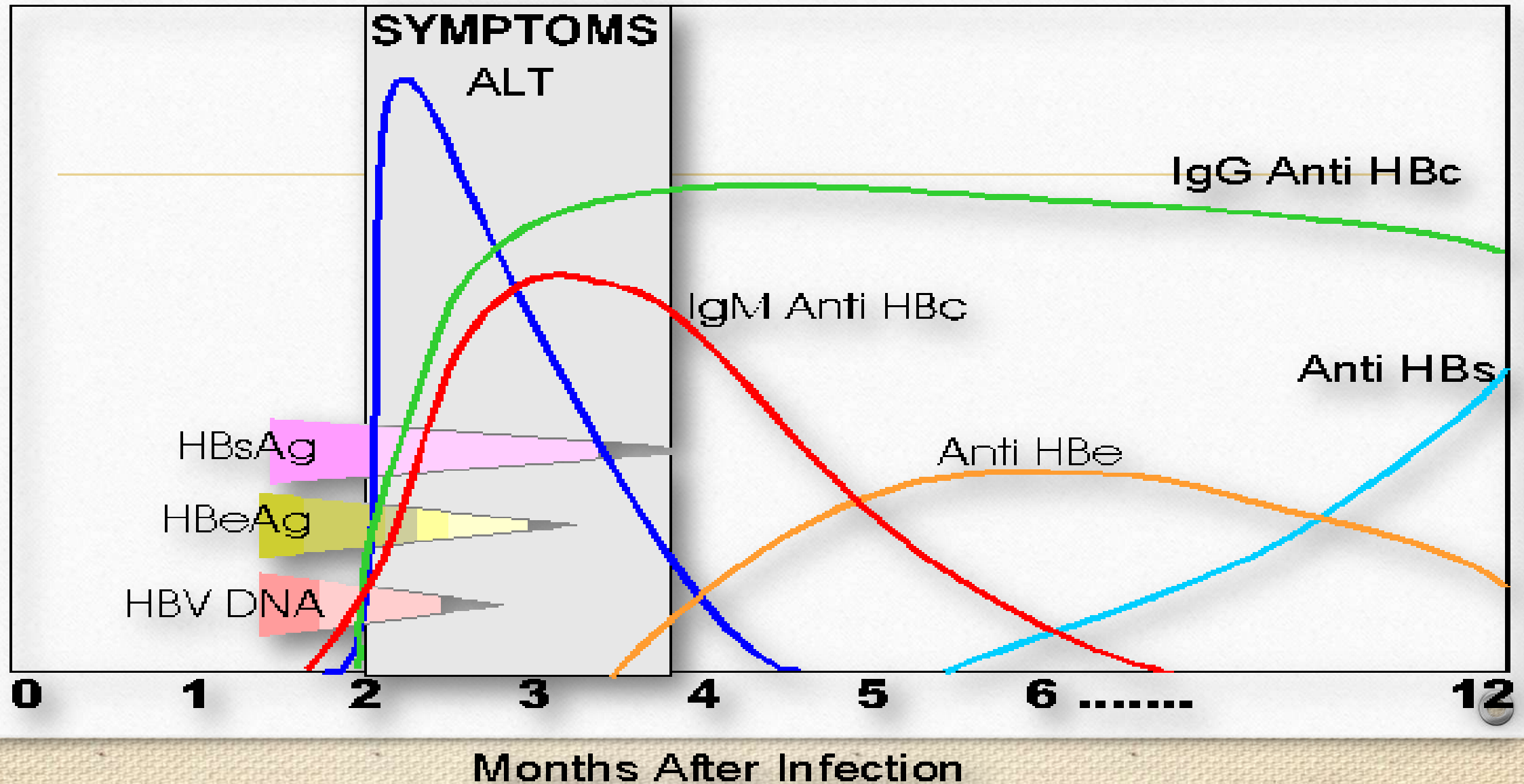


# HBV: EXTRAHEPATIC MANIFESTATIONS



# Making Sense of Serologies

# Natural Serologies after Acute HBV Infection



TEST	RESULT	INTERPRETATION
HBsAg HBsAb HBcAb	(-) (-) (-)	No infection; Susceptible
HBsAg HBsAb HBcAb	(-) (+) (+)	Immune due to natural infection
HBsAg HBsAb HBcAb	(-) (+) (-)	Immune
HBsAg HBsAb HBcAb IGG / IGM	(+) (-) (+) / (+)	Acute Infection
HBsAg HBsAb HBcAb IGG / IGM	(+) (-) (+) / (-)	Chronic infection
HBsAg HBsAb HBcAb	(-) (-) (+)	Interpretation Unclear; 4 Possibilities (1) Resolved infection ( most common) (2) False (+) anti-HBc, susceptible to infection (3) Low level chronic infection (4) Resolving acute infection

## Definitions

Chronic hepatitis B - **C**hronic necroinflammatory disease of the liver caused by persistent infection with hepatitis B virus. Chronic hepatitis B can be subdivided into HBeAg positive and HBeAg negative chronic hepatitis B.

Inactive HBsAg carrier state -- Persistent HBV infection of the liver without significant, ongoing --necroinflammatory disease

Resolved hepatitis -- Previous HBV infection without further virologic, biochemical or histological evidence of active virus infection or disease

Acute exacerbation or flare of hepatitis B -- Intermittent elevations of aminotransferase activity to more than 10 times the upper limit of normal and more than twice the baseline value

Reactivation of hepatitis B -- Reappearance of active necroinflammatory disease of the liver in a person known to have the inactive HBsAg carrier state or resolved hepatitis B

HBeAg clearance -- Loss of HBeAg in a person who was previously HBeAg positive

HBeAg seroconversion - Loss of HBeAg and detection of anti-HBe in a person who was previously HBeAg positive and anti-HBe negative

HBeAg reversion -- Reappearance of HBeAg in a person who was previously HBeAg negative, anti-HBe positive

# ***Chronic hepatitis B***

1. HBsAg 6 months
2. Serum HBV DNA 20,000 IU/ml ( $10^5$  copies/ml), lower values 2,000-20,000 IU/ml ( $10^4$ - $10^5$  copies/ml) are often seen in HBeAg-negative chronic hepatitis B
3. Persistent or intermittent elevation in ALT/AST levels
4. Liver biopsy showing chronic hepatitis with moderate or severe necroinflammation

## ***Inactive HBsAg carrier state***

1. HBsAg 6 months
2. HBeAg-, anti-Hbe
3. Serum HBV DNA 2,000 IU/m
4. Persistently normal ALT/AST levels
5. Liver biopsy confirms absence of significant hepatitis

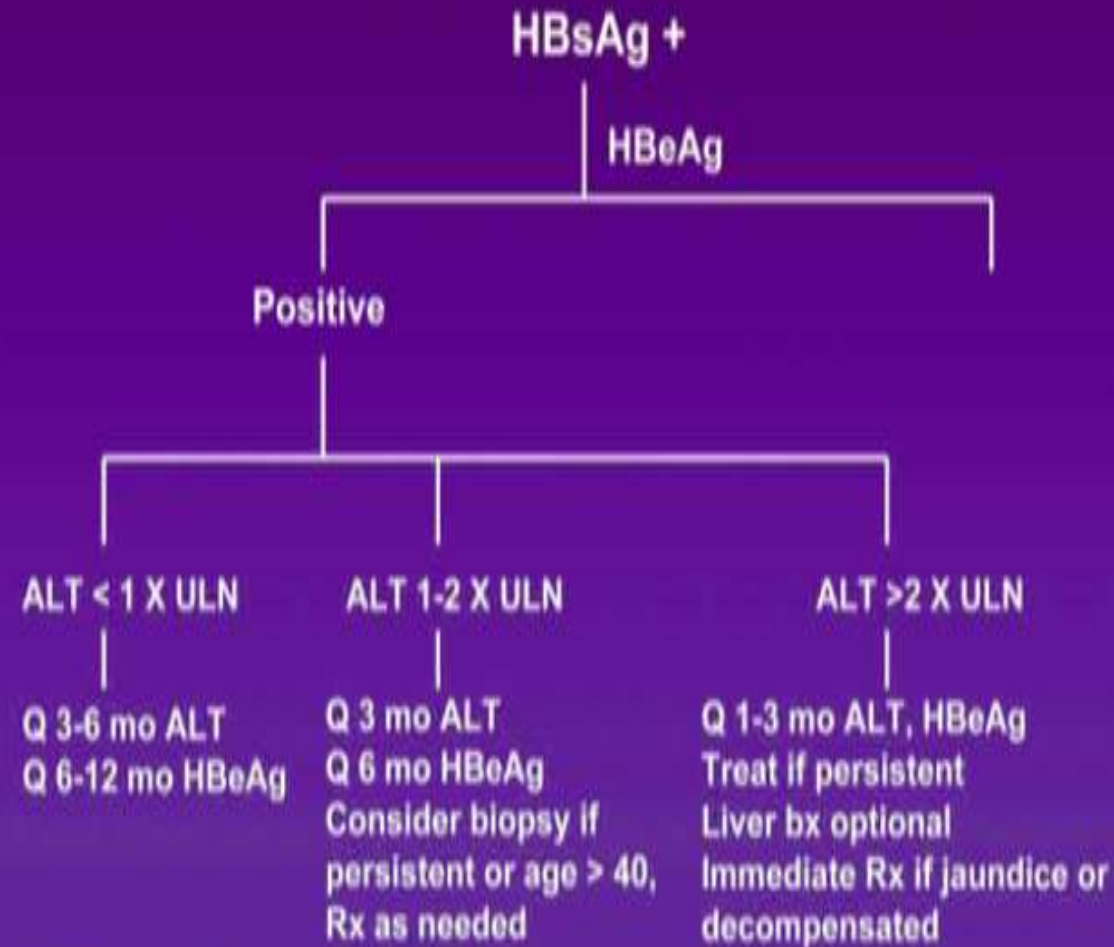
## ***Resolved hepatitis B***

1. Previous known history of acute or chronic hepatitis B or the presence of anti-HBc anti-HBs
2. HBsAg (-)
3. Undetectable serum HBV DNA#
4. Normal ALT levels

## **Factors Associated with Progression of HBV-related Liver Disease**

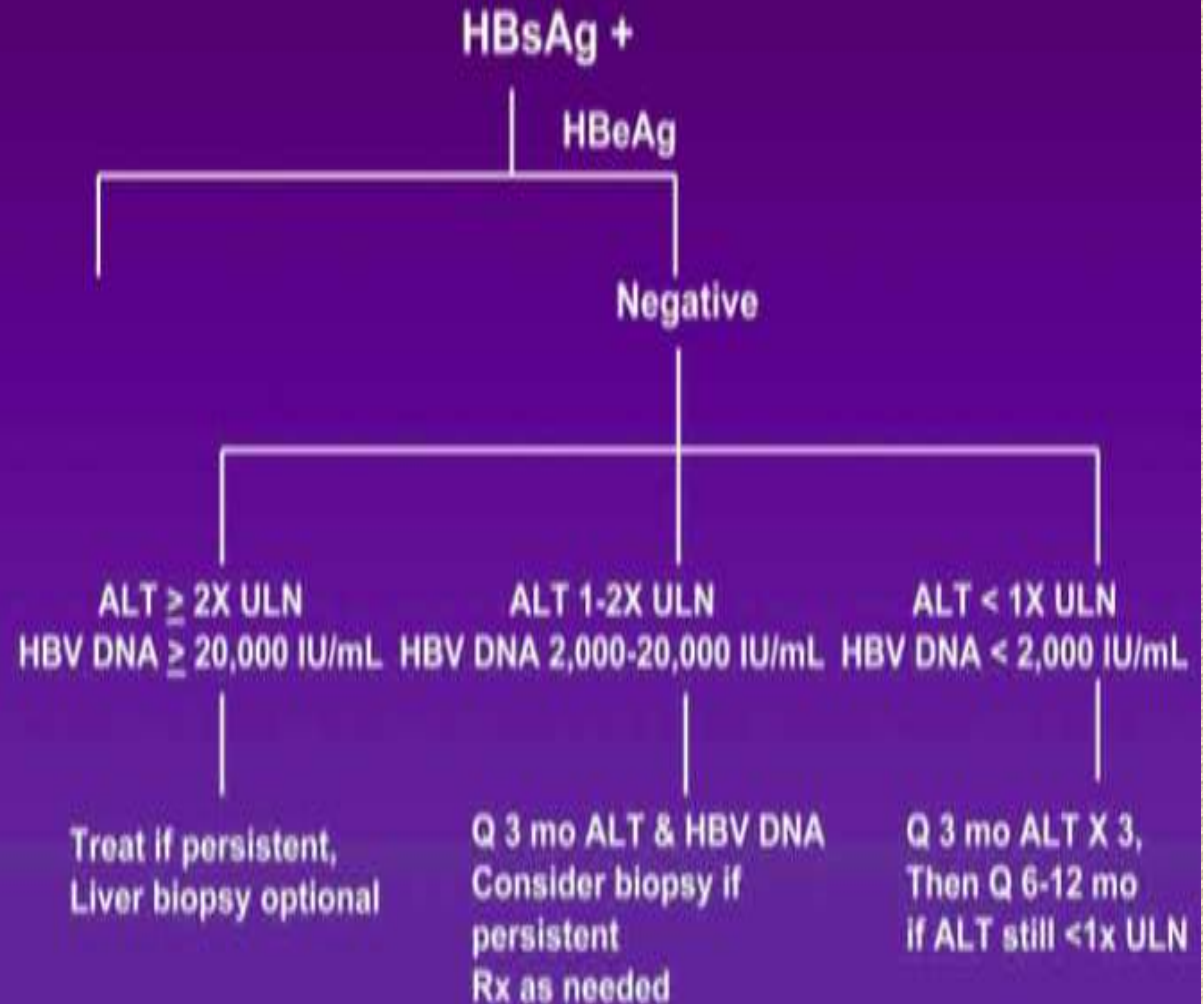
- older age (longer duration of infection)
- HBV genotype C
- high levels of HBV DNA
- habitual alcohol consumption
- smoking
- concurrent infection with HCV, HDV or HIV
- Male gender
- Reversion from HBeAg (-) to (+)

## A Management of Chronic HBV Infection\*



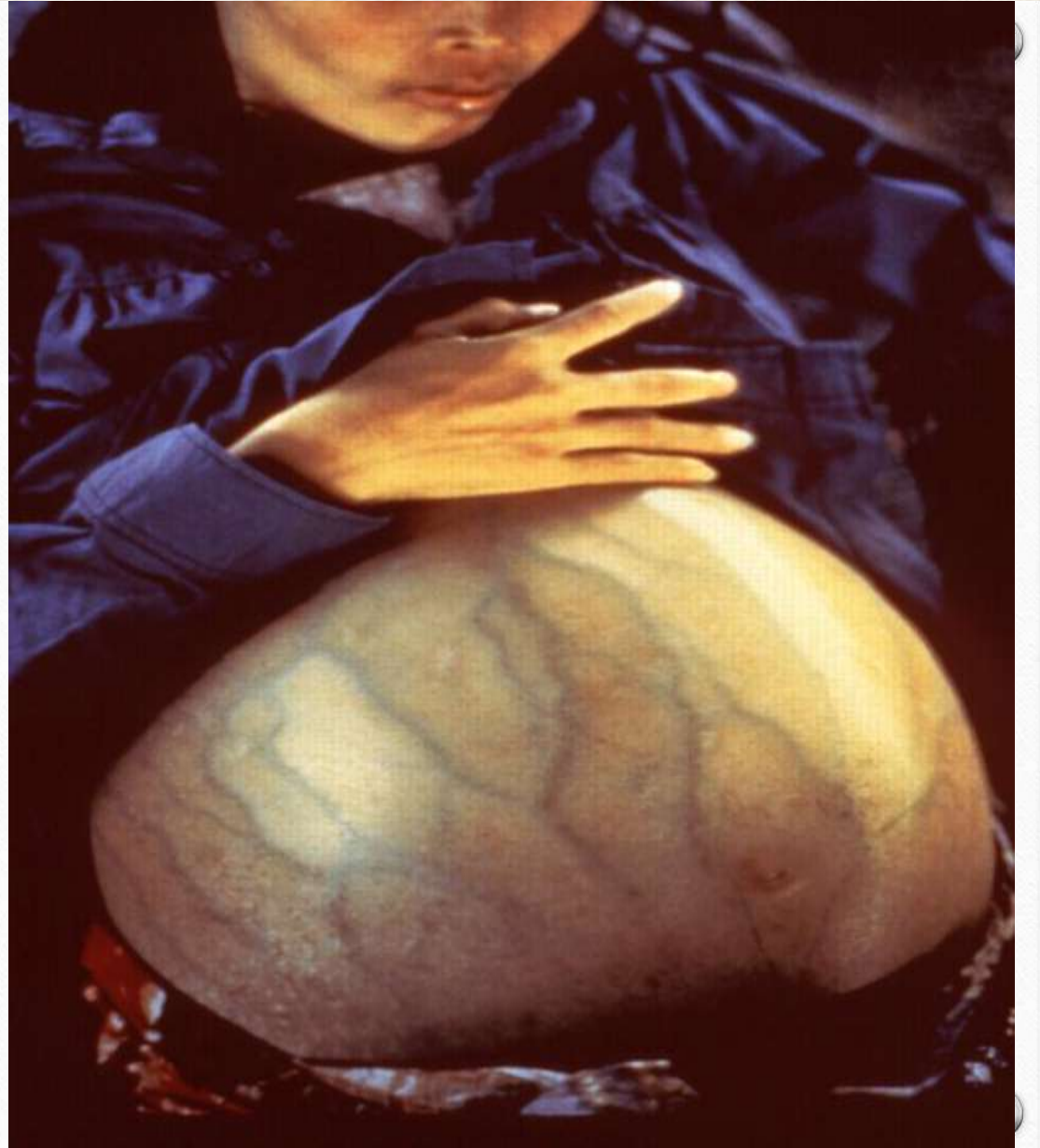
\* HCC surveillance if indicated

## B Management of Chronic HBV Infection\*



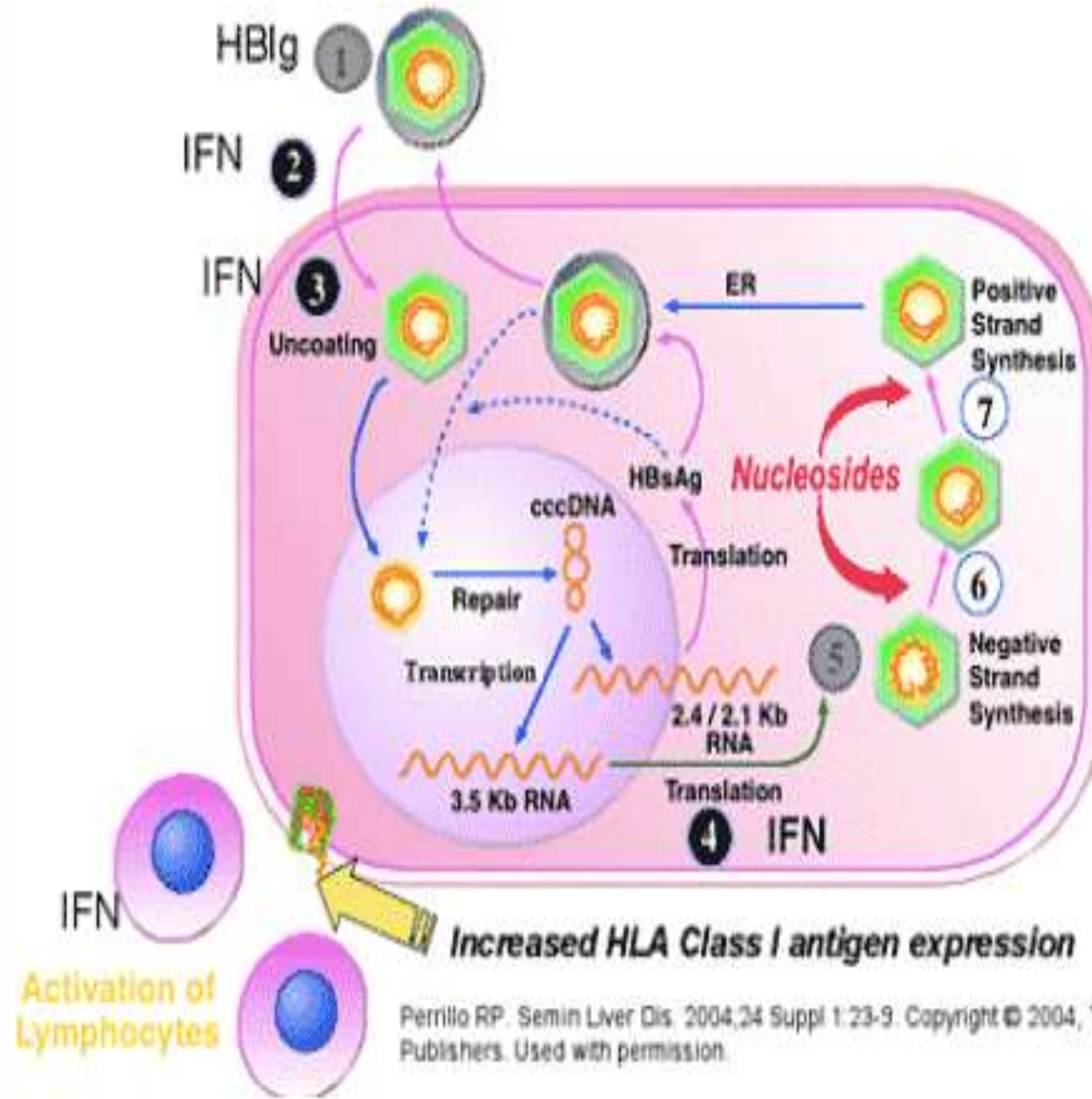
\* HCC surveillance if indicated

# Treatment of Chronic HBV



# Hepatitis B Life Cycle

## Targets for Treatment Agents



Perrillo RP. Semin Liver Dis. 2004;24 Suppl 1:23-9. Copyright © 2004, Thieme Medical Publishers. Used with permission.

# Goals of Treatment

- To prevent death by liver failure
- To prevent development of Hepatocellular Carcinoma
- To improve the quality of life of those with liver disease

# Endpoints of Treatment

- HBeAg seroconversion
- Elimination of detectable virus
- ALT < 0.5 ULN

# INTERFERON ALPHA (cytokine) including pegylated IFN

- **Mechanism**      **Induces antiviral state via induction of cellular genes**
- **Route**              **Must be given parenterally**
- **Adverse Effects**      **Flu-like symptoms; Hematologic, neurologic, Hepatic, and renal toxicity**
- **Indications**              **Chronic HBV & HCV    HPV & HHV8 infections**

# NUCLEOS(T)IDE ANALOGS FOR TREATMENT OF CHRONIC HBV

*DNA POL/RT INHIBITORS (oral)*

<b>DRUG</b>	<b>YEAR Licensed</b>	<b>% HBV DNA(-) @ 1 year (eAg+ / eAg-)*</b>	<b>% Resistant @ 1 year (eAg+ / eAg-)</b>
Lamivudine	1998	36/72	24/21
Adefovir	2002	21/63	0/0
Entecavir	2005	67/90	<1/<1
Telbivudine	2006	60/88	4/3
Tenofovir	2008	76/93	0/0

\*25/63 for IFN, with no resistance

**Table 8. Responses to Approved Antiviral Therapies Among Treatment-naïve Patients with HBeAg Positive Chronic Hepatitis B**

	<b>Standard IFN-<math>\alpha</math> 5 MU qd or 10 MU tiw 12-24 wk</b>	<b>Control</b>	<b>Lamivudine 100 mg qd 48-52 wk</b>	<b>Placebo</b>	<b>Adefovir 10 mg qd 48 wk</b>	<b>Placebo</b>	<b>Entecavir 0.5 mg qd 48 wk</b>	<b>Telbivudine 600 mg qd 52 wk</b>	<b>PegIFN<math>\alpha</math> 180 mcg qw 48 wk</b>	<b>PegIFN<math>\alpha</math> + Lamivudine 180 mcg qw + 100 mg 48 wk</b>
Loss of serum HBV DNA*	37%	17%	40-44%	16%	21%	0	67%	60%	25%	69%
Loss of HBeAg	33%	12%	17-32%	6-11%	24%	11%	22%	26%	30%/34% <sup>@</sup>	27%/28% <sup>@</sup>
HBeAg seroconversion	Difference of 18%		16-21%	4-6%	12%	6%	21%	22%	27%/32% <sup>@</sup>	24%/27% <sup>@</sup>
Loss of HBsAg	7.8%	1.8%	<1%	0	0	0	2%	0%	3%	3%
Normalization of ALT	Difference of 23%		41-75%	7-24%	48%	16%	68%	77%	39%	46%
Histologic improvement	na	na	49-56%	23-25%	53%	25%	72%	65%	38% <sup>^</sup>	41% <sup>^</sup>
Durability of response	80-90%		50-80% <sup>#</sup>		~90% <sup>#</sup>		69% <sup>#</sup>	~80%	na	

\*Hybridization or branched chain DNA assays (lower limit of detection 20,000-200,000 IU/ml or 5-6 log copies/ml) in standard IFN- $\alpha$  studies and some lamivudine studies, and PCR assays (lower limit of detection approximately 50 IU/ml or 250 copies/ml) in other studies na = not available

<sup>@</sup>Responses at week 48 / week 72 (24 weeks after stopping treatment)

<sup>#</sup>Lamivudine and entecavir - no or short duration of consolidation treatment, Adefovir and telbivudine - most patients had consolidation treatment

<sup>^</sup>Post-treatment biopsies obtained at week 72

# NUCLEOS(T)IDE ANALOGS FOR TREATMENT OF CHRONIC HBV

## *Adverse Events/Toxicity*

**Lamivudine**      Fatigue, HA, abdominal pain, myalgia, nasal symptoms, pancreatitis

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**Adefovir**      Fatigue, HA, N, abdominal pain, Nephro- and hepatotoxicity

**Entecavir**      Lactic acidosis, HA, diarrhea, arthralgia, insomnia

**Telbivudine**      Lactic acidosis, myopathy, neuropathy

**Tenofovir**      Hepato- and nephrotoxicity

## **Approved HBV Antiviral and Interferon Therapy Cost Comparison 2010\***

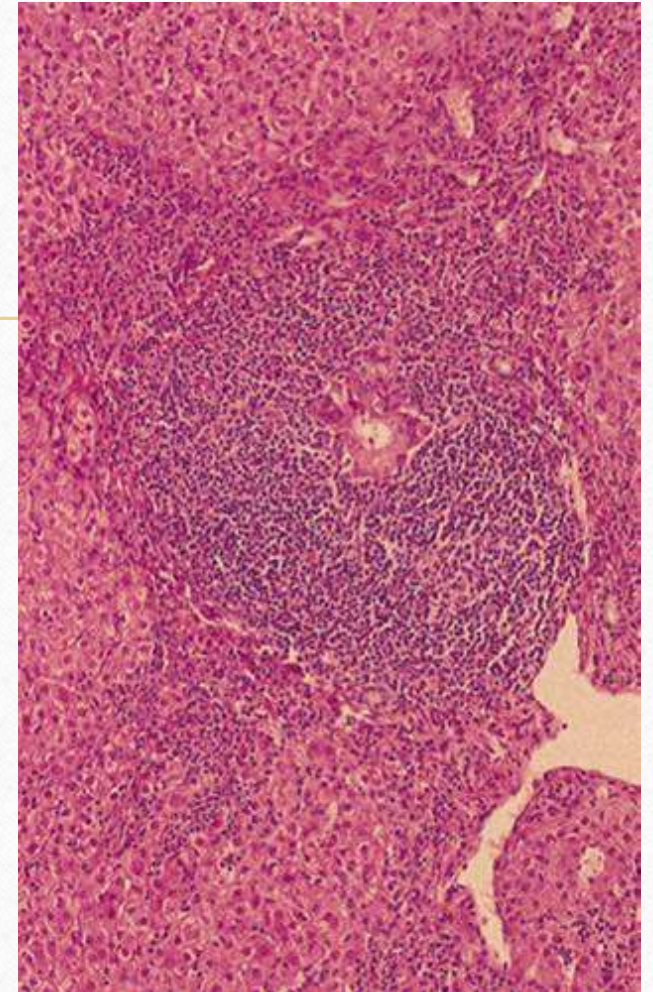
<b>Drug Name</b>	<b>Average Monthly Cost</b>	<b>Annual Cost</b>
<b>Lamivudine 100 mg (Epivir-HBV)</b>	<b>\$269.83</b>	<b>\$3,237.96</b>
<b>Adefovir 10 mg (Hepsera)</b>	<b>\$967.33</b>	<b>\$11,607.96</b>
<b>Entecavir 0.5 mg (Baraclude)</b>	<b>\$928.84</b>	<b>\$11,146.08</b>
<b>Tenofovir 300 mg (Viread)</b>	<b>\$813.35</b>	<b>\$9,760.20</b>
<b>Telbivudine 600mg (Tyzeka)</b>	<b>\$800.89</b>	<b>\$9,610.68</b>
<b>Interferon (Intron-A) 5 mil. IU Kit</b>	<b>\$1,283.38</b>	<b>\$15,400.56</b>
<b>10 mil. IU Kit</b>	<b>\$2,002.73</b>	<b>\$24,032.76</b>
<b>Pegylated Interferon (Pegasys) 180 mcg/0.5ml Kit</b>	<b>\$2,169.43</b>	<b>\$26,033.16</b>

\*Averages based on 2010 midyear wholesale costs obtained from Drugstore.com, Target Pharmacy, and Walgreen's Pharmacy

Antiviral treatment sources: Target, Walgreens, drugstore.com. Interferon source: drugstore.com

# Principles of treatment

- Tenofovir & entecavir preferred for initial Rx.
- Combination therapy for:
  - HIV/HBV coinfection
  - patients with drug resistance and with decompensated cirrhosis
- Indications for therapy:
  - High HBV DNA levels and elevated ALT levels
  - HIV



# New Drugs in development

- Clevudine –DNA polymerase inhibitor (approved in S. Korea)
- Besifovir – DNA polymerase inhibitor (Phase II trials, S. Korea)
- AGX-1009 – Prodrug of Tenofovir (Phase I in China)
- Nov-205 – Non-nucleoside protein production inhibitor (approved in Russia)
- Myrcludex – entry inhibitor (approved for post-transplant patients)
- Hap compound – inhibit viral nucleocapsid (Phase I)
- Rep 9AC – HBsAg release inhibitor (Phase I )
- Thymosin Alpha-1 – Immune stimulator ( approved for liver cancer)
- Interleukin-7 – Immunomodulator (Phase I/Iia)
- HBV Core Ag vaccine – therapeutic vaccine (Phase I)

# PREVENTION - HBV Vaccine

- *Inactivated HBV vaccine*
  - *all HIV patients should be checked for HBsAb, HBsAg, and HBcAb*

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- *If non-immune, ideally vaccinate when CD4 ct >200*
- *Should test for post-vaccination antibody*
  - *at least 1 month after third dose of vaccine*
  - *HBsAb should become positive*

# PREVENTION - HBV Vaccine

**TABLE 5. Hepatitis B vaccine schedules for children, adolescents, and adults\***

Age	Schedule
Children (1–10 yrs)	0, 1, and 6 mos <sup>†</sup> 0, 2, and 4 mos <sup>†</sup> 0, 1, 2, and 12 mos <sup>†§</sup>
Adolescents (11–19 yrs)	0, 1, and 6 mos <sup>†</sup> 0, 1, and 4 mos <sup>†</sup> 0, 2, and 4 mos <sup>†</sup> 0, 12, and 24 mos <sup>†</sup> 0 and 4–6 mos <sup>†**</sup> 0, 1, 2, and 12 mos <sup>†¶</sup>
Adults (≥20 yrs)	0, 1, and 6 mos <sup>**††</sup> 0, 1, and 4 mos <sup>**</sup> 0, 2, and 4 mos <sup>**</sup> 0, 1, 2, and 12 mos <sup>¶**</sup>

\* Children, adolescents, and adults may be vaccinated according to any of the schedules indicated, except as noted. Selection of a schedule should consider the need to optimize compliance with vaccination

† Pediatric/adolescent formulation.

¶ A 2-dose schedule of Recombivax-HB adult formulation (10 µg) is licensed for adolescents aged 11–15 years. When scheduled to receive the second dose, adolescents aged >15 years should be switched to a 3-dose series, with doses 2 and 3 consisting of the pediatric formulation administered on an appropriate schedule.

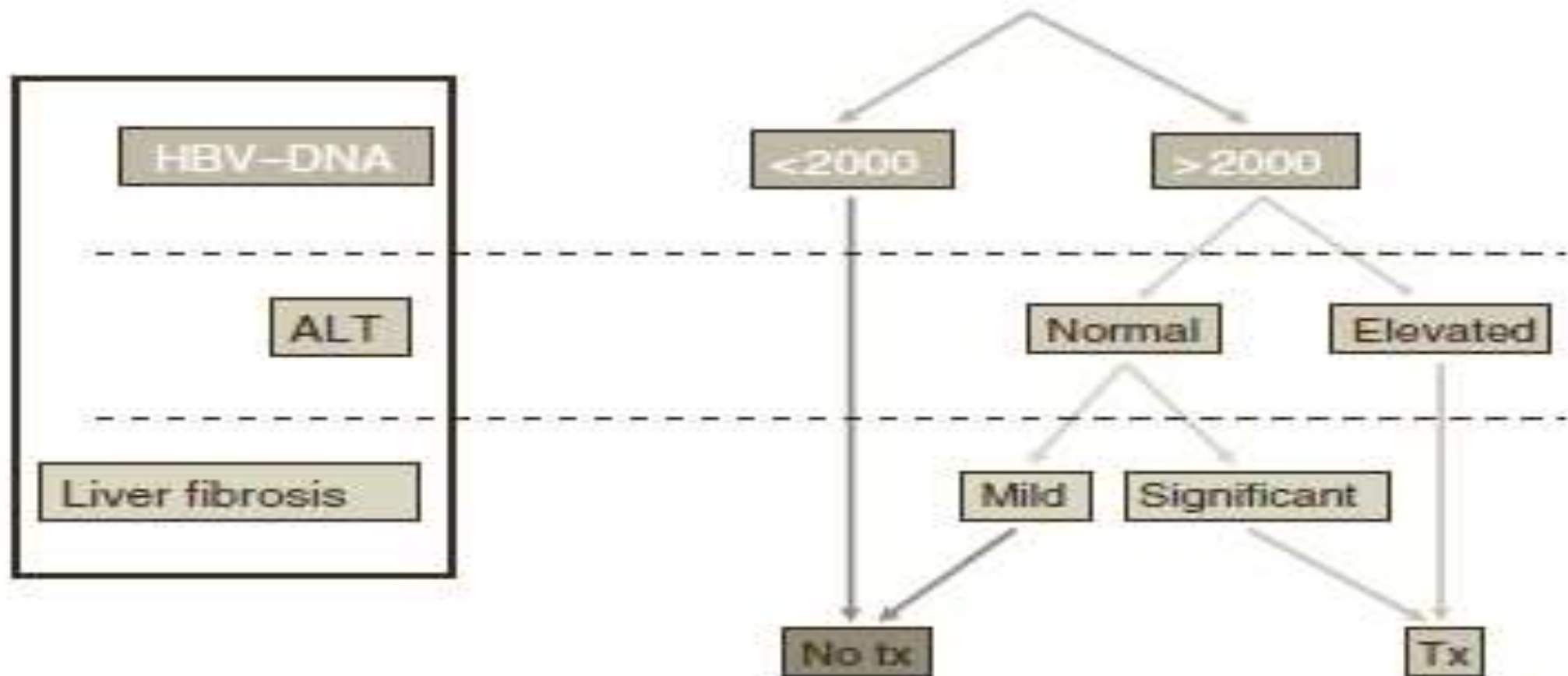
§ A 4-dose schedule of Engerix B is licensed for all age groups.

\*\* Adult formulation.

†† Twinrix may be administered to persons aged ≥18 years at 0, 1, and 6 months.

# Hepatitis B in HIV

- Higher levels of hepatitis B viremia
- Progression to chronic hepatitis B is approximately five times as fast as that among people infected with only HBV
- Higher risk of cirrhosis and hepatocellular carcinoma
- Higher liver-related mortality compared to those with HIV infection alone
- HIV immunosuppression can cause the loss of hepatitis B surface antibodies and reactivation to chronic hepatitis B
- At higher level of immunosuppression, there is poorer antibody response to vaccination
- Decreased response to interferon treatment
- More rapid emergence of lamivudine resistance



**Fig. 1. Therapeutic algorithm for chronic hepatitis B in HIV.** HBV-DNA is expressed in IU/ml. ALT, alanine aminotransferase; HBV, hepatitis B virus; Tx, treatment.

# Pearls to remember in HIV-HBV treatment

- CD4 > 500 is preferred when starting treatment for HBV
- Entecavir has some degree of anti-HIV activity and can induce M184V mutation in HIV – Do NOT use in HIV NOT on ART
- Start ART earlier in HIV patients that need HBV treatment – include HBV active agents – TDF & FTC or 3TC
- Adefovir or pIFN should be first line for HBV treatment in HIV patients NOT on ART
- Telvibudine should NOT be used alone because of possible resistance selection of M204I that confers 5 – 25 fold resistance by second year of treatment

Hepatitis C

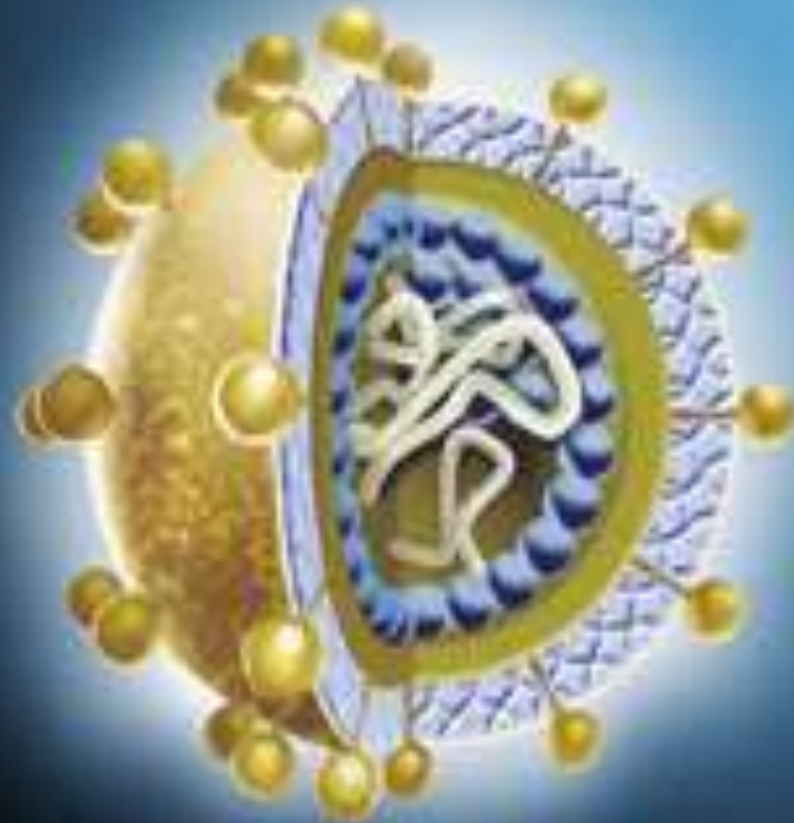
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Disease & Therapeutics

# HCV – the virus

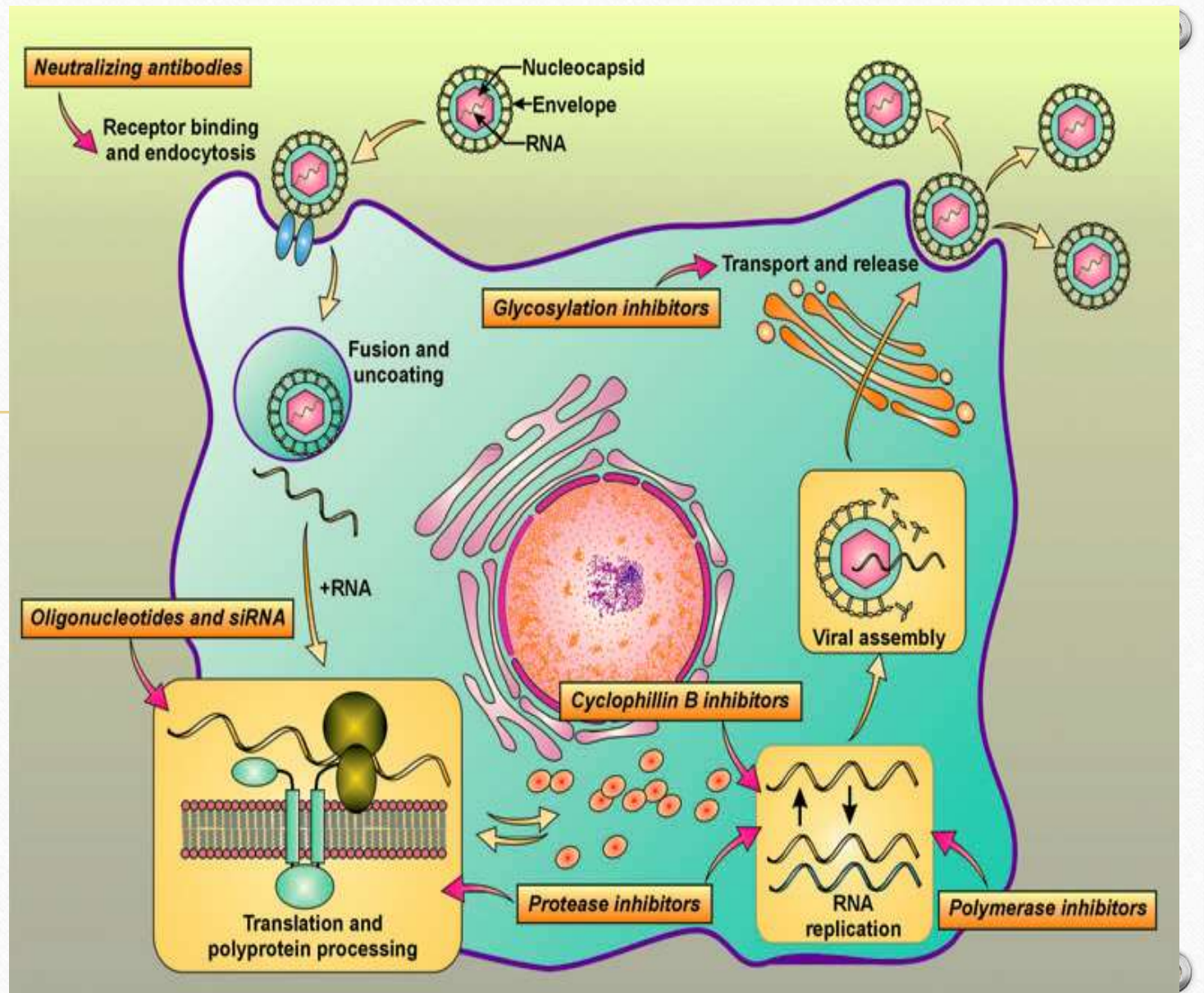
HCV is a flavivirus of the  
genus Hepacivirus

The particle consists of a  
core genetic material  
(RNA), surrounded by a  
protective shell of proteins  
and further encased in a  
lipid envelop



# HCV the virus

## Life Cycle of the Hepatitis C Virus Potential Targets for Anti-Viral Therapy



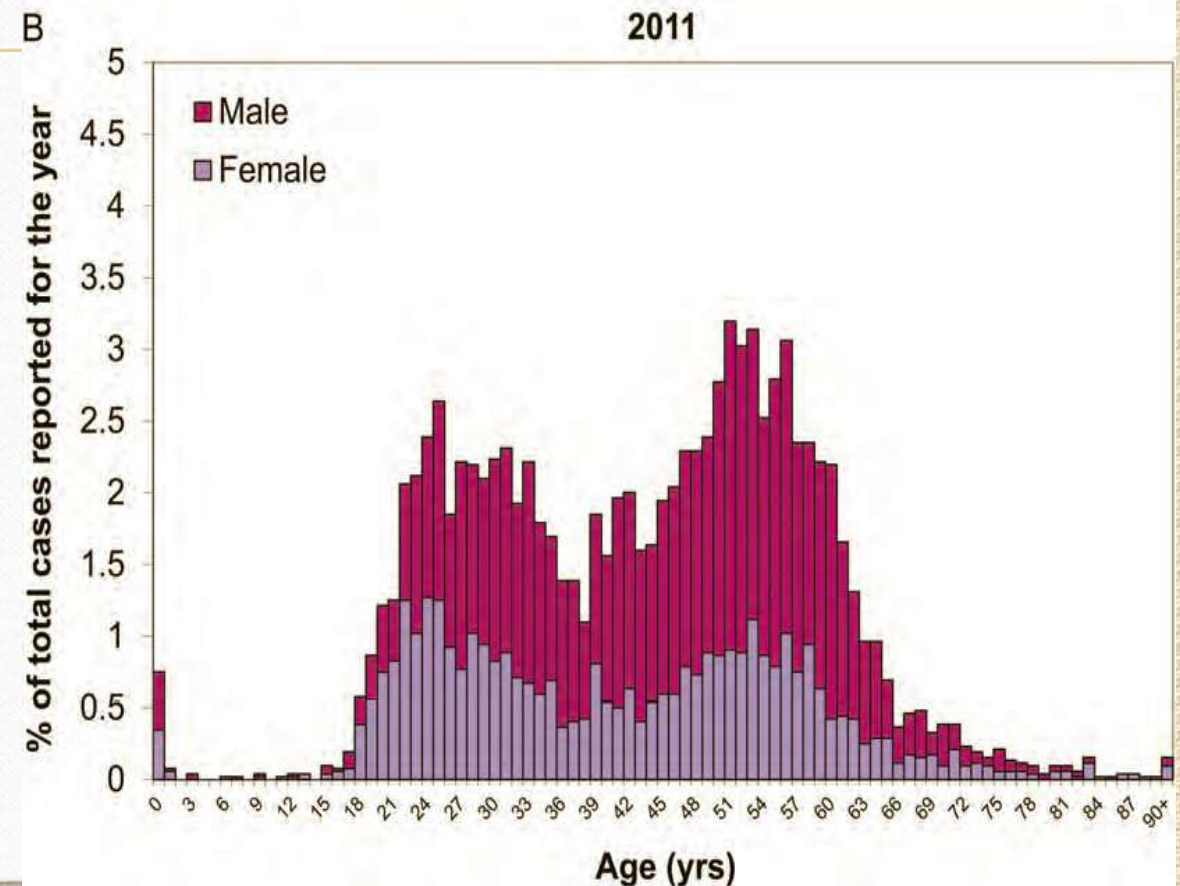
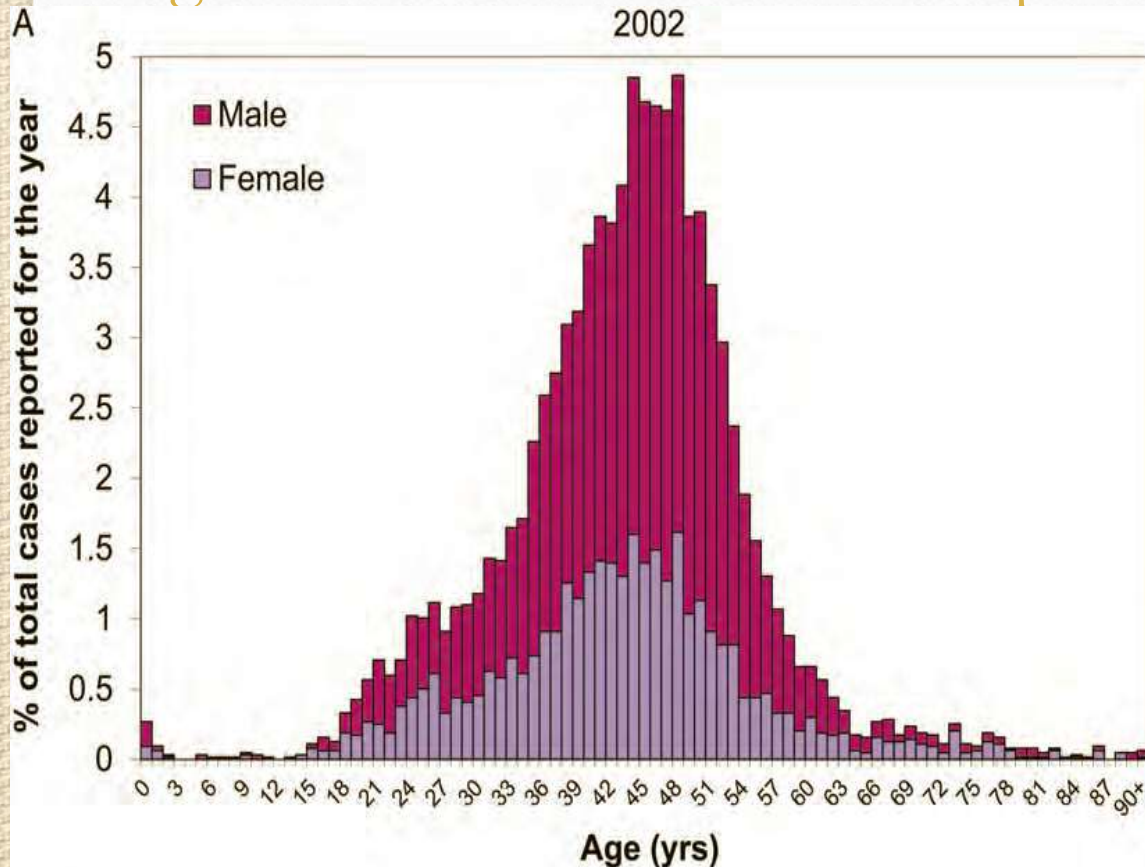
# HCV – Epidemiology

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- leading chronic blood-borne infection in the US
- In the US, approximately 3.9 million people are infected and 17,000 new cases yearly as of data current until 2010
- roughly 75% of those infected are the baby boomer generation (born between 1945-1965)
- about 170 million people are infected worldwide

# HCV – the Disease in HIV infected Adults

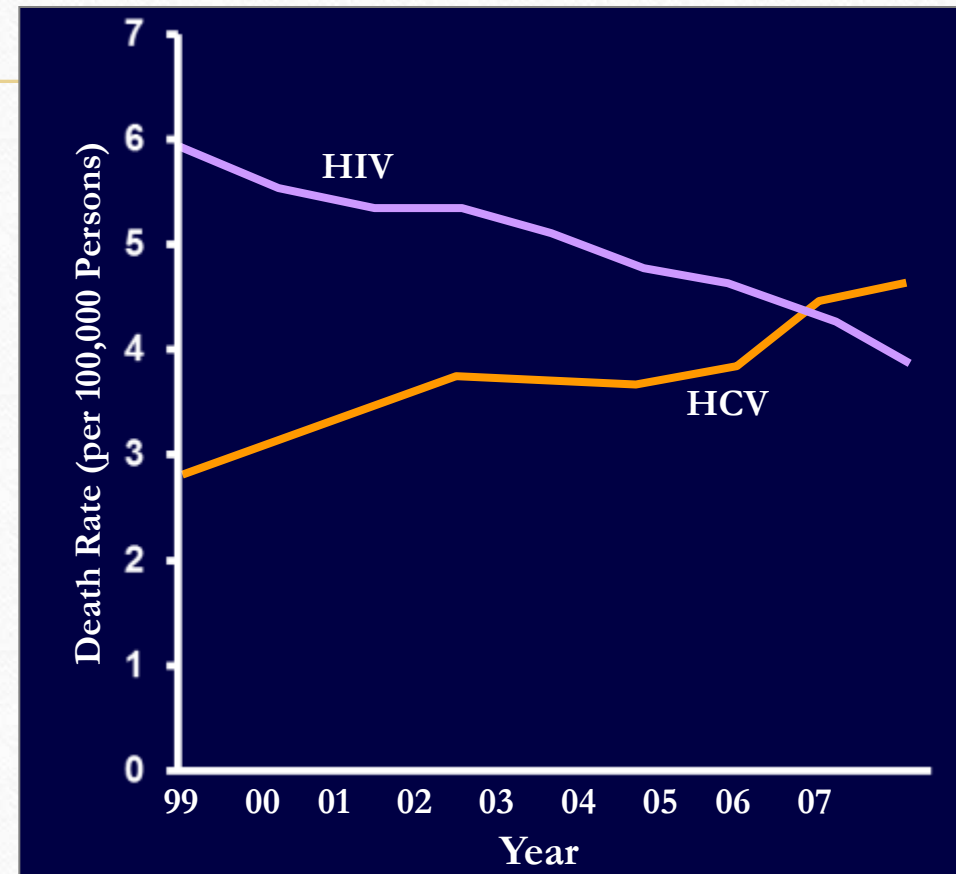
## Age Distribution of HCV seroprevalence in Massachusetts



# HCV and HIV Mortality in the US (1999-2007)

- US multiple-cause mortality data (NCHS, 50 states plus DC)
  - Death certificate data
  - Approximately 21.8 million decedents
- Change in age-adjusted mortality rates (per 100,000 person-years)
  - HCV: increased 0.18 ( $P=0.002$ )
  - HIV: decreased 0.21 ( $P=0.001$ )

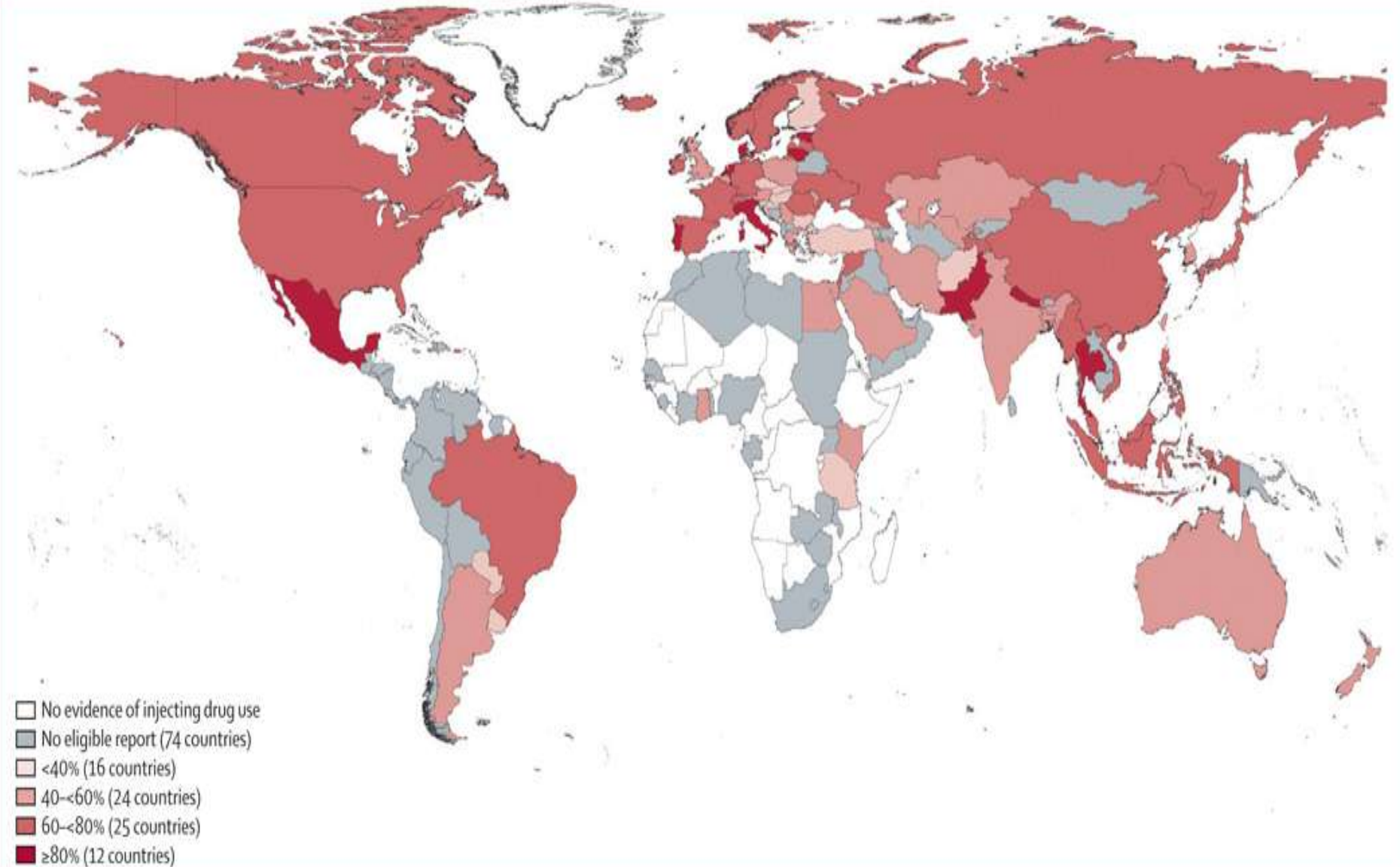
Annual Age-Adjusted Mortality Rates\*



National Center for Health Statistics  
\*HIV and listing of type of infection was counted for each type of infection

HCV – the  
disease

Prevalence  
of anti-  
HCV in  
Injection  
Drug  
Users



# Hepatitis C facts

Modes of transmission

parenteral, perinatal, sexual

Incubation period

3-12 weeks

Chronic infection

< 25 years --- 56 %

≥ 25 years -- 87 %

Premature mortality from ESLD

30 %

Survival outside the body

can survive outside the body at room  
temperature, on environmental surfaces,  
for at least 16 hours but no longer than 4  
days.

Transmission in body fluids

Blood and serum

Perinatal transmission

5%

# HCV – the virus

---

- Very rapid viral replication producing  $10^{10}$  -  $10^{12}$  virions/day
- It has a predicted viral half-life of 2 -3 hours
- Replication is inefficient resulting in numerous mutant strains coexisting with the dominant strain
- It is significantly more infective than HIV

# Hepatitis C – the disease

## Transmission

---

- Blood and blood products transfusion prior to 1992
- Needle sharing – IVDU/ Tattoo
- Mother to child perinatal transmission
- Hemodialysis
- Sex with  $\geq 20$  partners has a 4.5% increase chance of testing (+)

# HCV – the disease

## Who Should Be Tested For Hepatitis C?

New, expanded recommendation:

*All persons born from 1945 through 1965*

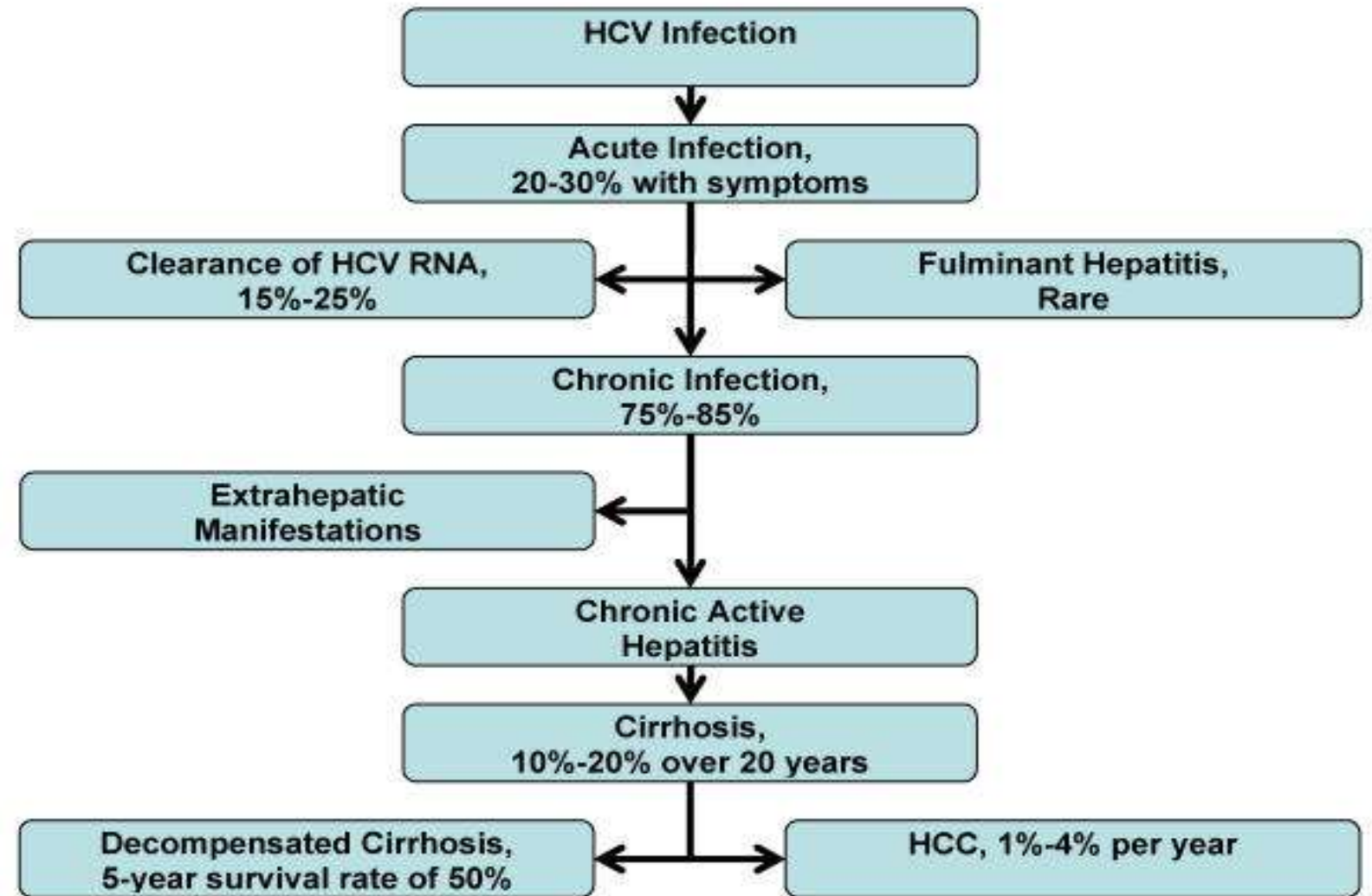
Existing, risk-based guidelines:

---

- Anyone who has ever injected illegal drugs
- Recipients of blood transfusions or solid organ transplants before July 1992, or clotting factor concentrates made before 1987
- Patients who have ever received long-term hemodialysis treatment
- Persons with known exposures to hepatitis C, such as:
  - Health care workers after needlesticks involving blood from a patient with hepatitis C
  - Recipients of blood or organs from a donor who later tested positive for hepatitis C
- People living with HIV
- People with signs or symptoms of liver disease (e.g., abnormal liver enzyme tests)
- Children born to mothers who have hepatitis C

# HCV – the disease

## Natural History of HCV Disease



# HCV: Extrahepatic Manifestations

## Autoimmune Phenomena

- CRST Syndrome<sup>2</sup>

## Dermatologic

- Cutaneous Necrotizing Vasculitis<sup>2</sup>
- Lichen Planus<sup>1</sup>
- Porphyria Cutanea Tarda<sup>1</sup>

## Hematologic

- Aplastic Anemia<sup>1</sup>
- Mixed Cryoglobulinemia<sup>1</sup>
- Non Hodgkin's B-Cell Lymphoma<sup>1</sup>
- Thrombocytopenia<sup>1</sup>

## Endocrine

- Diabetes Mellitus<sup>2</sup>
- Hypothyroidism<sup>2</sup>



## Neuromuscular

- Arthritis/Arthralgia<sup>3</sup>
- Myalgia/Weakness<sup>3</sup>
- Peripheral Neuropathy<sup>3</sup>

## Neuropsychiatric

- Depression<sup>4</sup>

## Ocular

- Corneal Ulcer<sup>2</sup>
- Uveitis<sup>2</sup>

## Renal

- Glomerulonephritis<sup>1</sup>
- Nephrotic Syndrome<sup>2</sup>

## Vascular

- Necrotizing Vasculitis<sup>3</sup>
- Polyarteritis Nodosa<sup>3</sup>

CRST = Calcinosis, Raynaud's phenomenon, Sclerodactyly and Telangiectasis

1. Angello V, et al *Journal of Hepatology*. 2004;40:341-352
2. Galossi A, et al. *J Gastrointest Liver Dis*. 2007; 16:65-73
3. NIH. *NIH Consensus State Sci Statements* 2002; 19(3): 1-46
4. Scene D, et al. *Metab Brain Dis*. 2004;19: 357-381

# HCV – the disease in HIV infected adults

- Up to 25% of the approximately 1.2 million people infected with HIV-1 in the United States also have HCV
- HCV related liver disease is accelerated in the presence of HIV
- Alcohol use disorder is common in coinfecting adults with prevalence of 30-50%
- Viral hepatitis (mostly HCV) is the most likely cause of non-AIDS death in persons living with HIV

# HCV – the disease in HIV infected Adults

- Host is immunosuppressed ➡ allows for unusual high levels of viral replication and viral protein expression ➡ **HCV may induce direct hepatocellular damage**<sup>1</sup>
- Majority of co-infected patients acquired their HCV infection while they are still immune-competent. Their disease course follows the same pattern as the mono-infected HCV patient, albeit at a faster rate of progression (**26 years to cirrhosis vs. 34 years for HCV mono-infected**)<sup>2</sup>
- For HIV patients who acquired their infection when they were already immune-compromised (**hi HIV VL and low CD4**), they suffer a highly accelerated clinical course ➡ about 1-2 years to cirrhosis from initial infection and roughly 8 years to death because of liver failure.<sup>2</sup>

# HCV – treatment goals

---

- To prevent death by liver failure
- To prevent development of Hepatocellular Carcinoma
- To prevent progression to liver failure to the point of needing liver transplant
- To improve the quality of life of those with liver disease

# Poor Prognostic Factors

---

1. HIV co-infection
2. HAV co-infection
3. HBV co-infection
4. Alcohol consumption
5. BMI  $\geq 25$

# Initial Screening

---

- (+) HCV serology
- H&P (within the last 12 mos)
- Labs : CBC, CMP, PT/INR, AFP, HIV,HBV,HAV serologies
- PPD and TB chemoprophylaxis as necessary
- Vaccinations, as indicated (HAV,HBV, Influenza)

## Co-Morbidities considered stable for treatment

1. DM – A1C < 8.0
2. NO seizure activity in the last 12 months
3. Clinically / Chemically Euthyroid
4. CAD : No Chest pain or acute episode in the last 12 mos.
5. Connective Tissue Ds – inactive (ESR &/or CRP WNL)
6. Anemia resolved (w/o CAD: Male Hb  $\geq$  13; Female  $\geq$  12; W/ CAD Hb  $\geq$  14)
7. Platelet  $\geq$  75,000
8. ANC (absolute neutrophil count)  $\geq$  1,500
9. Serum Creatinine < 2.0
10. NO hemoglobinopathies (thalassemia, sickle cell ds)
11. NO moderate to severe asthma/COPD, steroid-dependent
12. NO solid organ recipient (kidney, lung, heart)
13. NOT pregnant
14. NO GI autoimmune disease (Crohn's, Ulcerative colitis, primary biliary cirrhosis, autoimmune hepatitis)
15. NOT on Warfarin, Clopidogel (PLAVIX)
16. Normal Protein S and Protein C activity for those with H/o DVT
17. Mental Health problems controlled on medications

# Factors to consider when starting treatment

## Laboratory Test or Exam

- Degree of liver fibrosis
- HCV genotype
- HCV RNA
- Baseline funduscopy examination

## Implications in TX

- Timing of treatment
- Duration of treatment and choice of Drugs
- Baseline level for monitoring response to treatment
- For those at risk for ophthalmologic complication (DM; HTN in age group  $\geq 50$ )

## Grading of Fibrosis

- **Early Fibrosis** – METAVIR stage 0 – 1; LUDWIG-BATTS Stage 0 – 1; ISHAK Stage 0 – 2
- **Significant Fibrosis** – METAVIR Stage 2 – 4; LUDWIG-BATTS Stage 2 – 4; ISHAK Stage 3 – 6
- **Cirrhosis** – METAVIR Stage 4; LUDWIG-BATTS Stage 4; ISHAK Stage 5 – 6

# Treatment Options

- Pegylated  $\alpha$ -Interferon or pegInterferon
- Ribavirin
- Direct Acting Agents

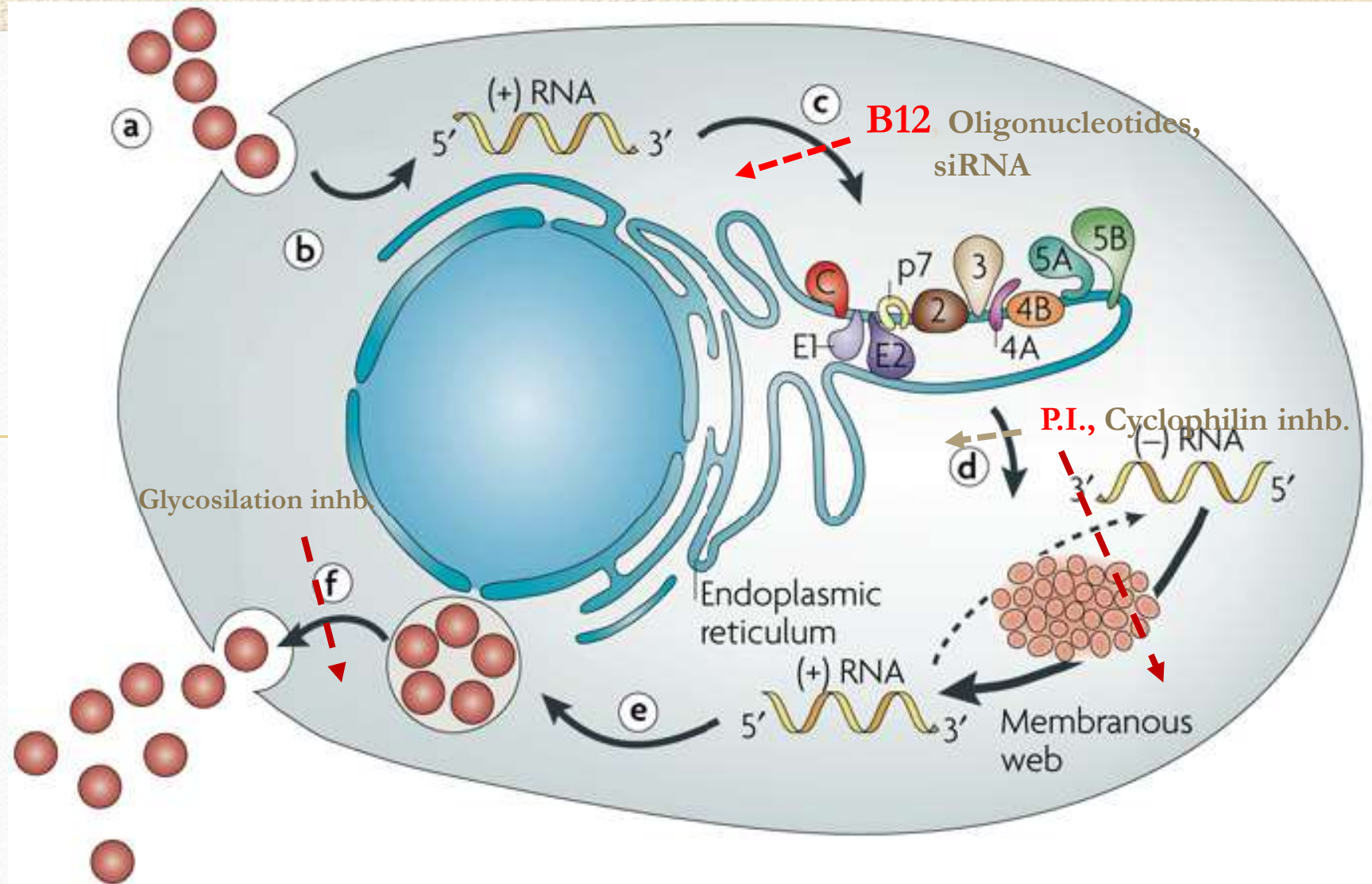
Telaprevir

Boceprevir

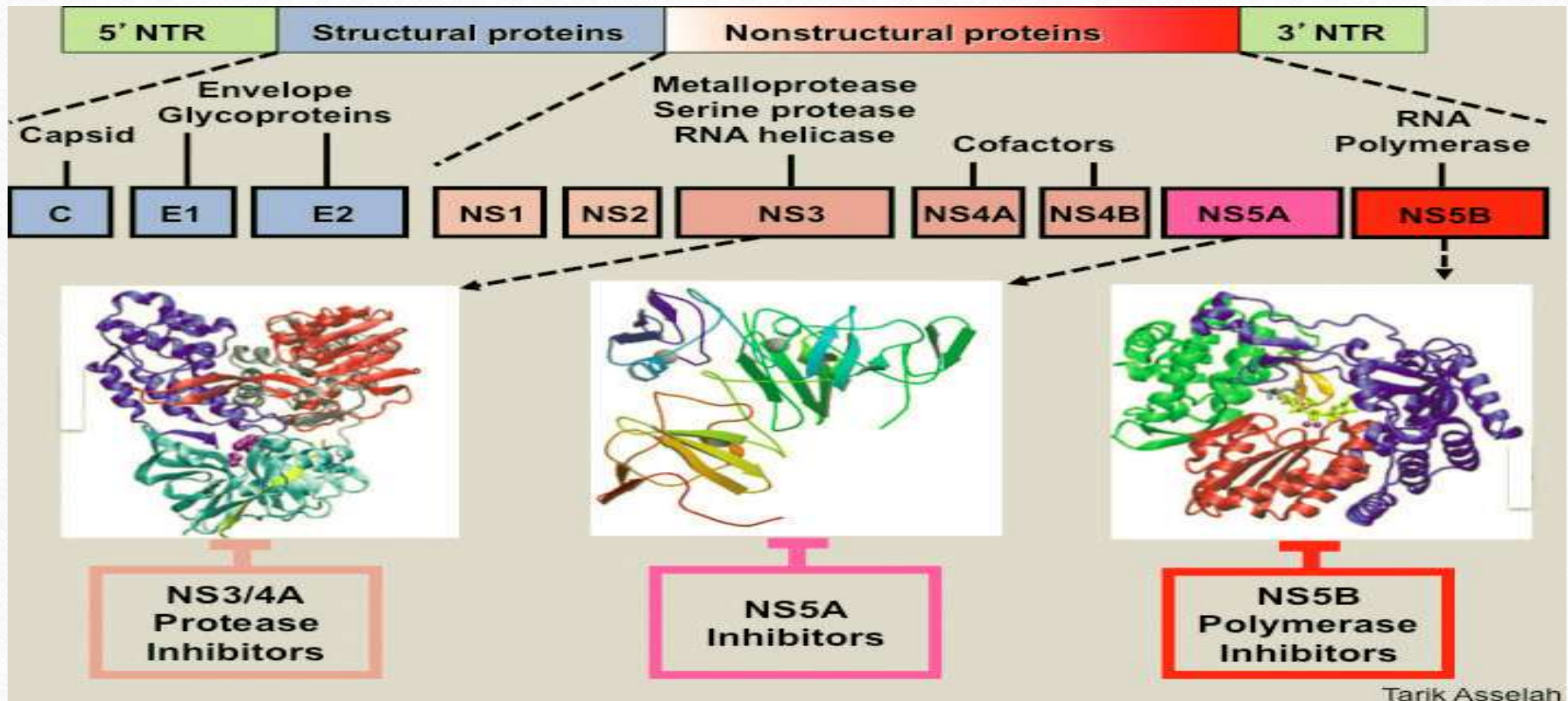
Vitamin B12

## HCV virion production

## Potential Targets for Antiviral Treatment



# HCV Polyprotein String



HCV Enzymes as Potential Target for Antiviral Agents

# Definition of Terms

---

- RVR (Rapid Virologic Response) – U/D HCV RNA at week 4
- EVR (Early Virologic Response) – U/D HCV RNA at week 12
- ETR (End of Treatment Response) – U/D HCV RNA at end of treatment
- SVR (Sustained Virologic Response) – U/D HCV RNA 6 months after Tx
- Null Response -  $<2$  log decrease at week 12 or detectable HCV RNA at week 24
- Partial Response -  $>2$  log decrease at week 12 but detectable HCV RNA at week 24
- Relapse – loss of HCV RNA at any point in the treatment and reversion to detectable

# PegInterferon

- Mechanism of Action – activates the immune system into an antiviral state
- 

- Duration of Treatment (weeks) using IFN

Genotype 2 & 3	24 weeks
----------------	----------

Genotype 1, 4, 5, 6	48 weeks
---------------------	----------

HIV coinfectd	48 weeks regardless of genotype
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- Dose

Peginterferon alfa 2a	180 ug injected SQ (subcutaneously) once every week
-----------------------	---

Peginterferon alfa 2b	1.5 mcg/kg/week
-----------------------	-----------------

# PegInterferon alfa 2a

## Dosage Adjustments

135 mcg      ANC < 750 /ml  
Moderate depression  
ALT increase above baseline

90 mcg      PLT < 50 x1000/ml

## Discontinue / Hold

ANC < 500, hold till ANC returns to >1000, resume at 90 ug

PLT < 25 x 1000/ml

Severe Depression

Progressive increase of ALT or with increased TBil or hepatic decompensation  
(encephalopathy, ascites, pedal edema)

# Peginterferon alfa 2b

## Dosage Adjustments

Reduce by 50%      Hb 8.5 – 10  
ANC < 750

---

## Discontinue / Hold

Hb < 8.5

ANC < 500, hold until ANC returns to 1000, resume at 50%

PLT < 50 x 1000/ml until resolved

Severe Depression

Progressive increase of ALT or with increased TBil or hepatic decompensation (encephalopathy, ascites, pedal edema)

# PegInterferon

## Stopping Rules

---

- Week 4                      <1 log decrease in HCV RNA
- Week 12                    <2 log decrease in HCV RNA
- Week 24                    Detectable HCV RNA

# PegInterferon

## **Side effects profile**

**Bone marrow depression – anemia, neutropenia, thrombocytopenia**

**Depression**

**Thyroid hormone abnormalities**

**Influenza-like sxs (fever, body ache, malaise)**

**Hair loss**

**Anorexia**

**Retinopathy**

**Vision loss (NAION) – rare but reported**

# Ribavirin

- **MOA – Unclear but it accelerates clearance of infected cells, prevents viral breakthrough during tx and relapse after treatment**
- 

- **Duration of Treatment (weeks) – same as pIFN**

- **Dosage (200 mg tablet)**

HCV geno 2 & 3

800 mg in 2 divided doses

HCV geno 1 & 4 <75 kg (165 lbs)

1000 mg in 2 divided doses

HCV geno 1 & 4  $\geq$  75 kg (165 lbs)

1200 mg in 2 divided doses

HCV/HIV coinfection

800 mg in divided doses

# Ribavirin

## Dosage Adjustment

Condition	Reduce to 600 mg / day	Discontinue
Patient with NO cardiac condition	Hb < 10 g/dL	Hb < 8.5 g/dL
Patient with H/O Stable cardiac condition	Decrease in Hb > 2 g/dL in any 4-week period	Hb < 12 g/dL despite 4 weeks of reduced doses

May restart at 600mg to 800 mg once critical value improve after 4 weeks

# Rivabirin

- Side effects profile
- 

Profound Anemia - hemolytic

Teratogenic

Pulmonary infiltrates

Acute coronary syndromes

# Boceprevir

- MOA – NS3 serine protease inhibitor
- Dose ( 200 mg tab)  
800mg TID given with light snack
- No dose adjustment for anemia, mild hepatic impairment (C-P score  $<6$ ), renal impairment
- Only approved for use in Genotype 1 infected patients

# Boceprevir Stopping Rules

## TX-Naïve

---

U/D at wk 8 & 24 – complete 28 wks of TT

(+) wk8, U/D wk 24 – complete 36wks TT + 12wks DT

## TX-experienced

U/D at wk8 & 24 – complete 36 wks of TT

(+) wk8, U/D wk24 – complete 36wks TT + 12wks DT

**VL  $\geq$  100 at wk8, Detectable at wk24 – STOP ALL TX**

# Boceprevir Side Effect Profile

---

- Fatigue 55%
- Anemia 45%
- Dysguesia 44%
- Nausea 43%
- Chills 33%
- Insomnia 30%
- Vomiting 28%
- Anorexia 26%
- Diarrhea 24%
- Alopecia 22%
- Dry Skin 22%
- Irritability 21%

# Telaprevir

- MOA – NS3 serine protein inhibitor
- Dose (375 mg tablet)  
750 mg (2 Tabs) TID given with 20 gm of Fat  
\* data showed BID dosing (3 tabs) equivalent efficacy with TID dosing
- No dose adjustment for anemia, mild hepatic impairment  
(C-P score < 6), renal impairment
- Only approved for use for genotype 1 infected patients

# Telaprevir

## Stopping Rules

---

### **TX-naïve and Relapser**

U/D at wk4 &/or wk12 – 12 wk TT + 12 wk DT

(+) <1000 at wk4 &/or wk12 – 12wkTT + 36wkDT

### **Prior Partial Responder & Null Responder**

12 wk TT + 36 wk DT

**$VL \geq 1000$  at wk 4 or 12 – STOP ALL TX**

# Telapravir Side Effect Profile

---

- Rash 56%
- Fatigue 56%
- Pruritus 47%
- Nausea 39%
- Anemia 36%
- Anorectal complaints 29%
- Diarrhea 26%

# Pretreatment Considerations for Telaprevir-Associated Rash

- Alert patient to risk of rash (56% of patients in phase III trials)<sup>[1]</sup>
  - Majority of case was mild to moderate<sup>[1]</sup>
  - 4% severe rash<sup>[1]</sup>
  - Can occur at any time during 12 wks of telaprevir<sup>[1]</sup>
- Good skin hygiene<sup>[2]</sup>
  - Emollient creams and lipid-rich lotions
  - Sunscreen, avoid prolonged sun exposure

# Grading of Telaprevir Rash



**Mild ( $\leq 25\%$  BSA)**



**Moderate (25% to 50% BSA)**



**Severe ( $> 50\%$  BSA)**

## Management Recommendations for Mild or Moderate Rash Due to Telaprevir

- **Monitor for systemic symptoms**
- **Continue all medicines**
  - **Do not dose reduce or discontinue TVR**
- **Watch for progression**
- **Continue good skin hygiene**
- **Consider topical steroids**
  - **Systemic steroids not recommended**
- **Consider oral antihistamines**

**Mild**



**Moderate**



# Management Recommendations for Severe Rash Associated With Telaprevir

- **Generalized rash involving either > 50% BSA or any of the following**

- Vesicles or bullae
- Superficial ulceration of mucous membranes
- Epidermal detachment
- Atypical or typical target lesions
- Palpable purpura, nonblanching erythema



- **Recommendations**
  - **Discontinue telaprevir**
    - If no better in 7 days (or early if indicated), discontinue RBV and/or pegIFN
    - Do not resume telaprevir
    - Remind patient that SVR is still possible
  - Good skin care practices
  - Oral antihistamines and/or topical corticosteroids
  - Consider referral to dermatologist

# Severe Skin Reactions Are Rare but Possible With Telaprevir Treatment



- In all patients with rash, monitor for
  - Stevens-Johnson syndrome
    - Fever, target lesions, mucosal erosions, or ulcerations
  - Drug reaction eosinophilia and systemic symptoms (DRESS)
    - Fever, facial edema, organ involvement (nephritis, hepatitis)
    - Eosinophilia may or may not be present
- Discontinue all medications immediately
- Refer for urgent medical care

# Medicines That Are Contraindicated With BOC and TEL

Drug Class*	Contraindicated With BOC <sup>[1]</sup>	Contraindicated With TEL <sup>[2]</sup>
Alpha 1-adrenoreceptor antagonist	Alfuzosin	Alfuzosin
Anticonvulsants	Carbamazepine, phenobarbital, phenytoin	N/A
Antimycobacterials	Rifampin	Rifampin
Antiretrovirals	EFV, all RTV-boosted PIs	DRV/RTV, FPV/RTV, LPV/RTV
Ergot derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Dihydroergotamine, ergonovine, ergotamine, methylergonovine
GI motility agents	Cisapride	Cisapride
Herbal products	Hypericum perforatum (St John's wort)	Hypericum perforatum
HMG CoA reductase inhibitors	Lovastatin, simvastatin	Lovastatin, simvastatin
Oral contraceptives	Drospirenone	N/A
Neuroleptic	Pimozide	Pimozide
PDE5 inhibitor	Sildenafil or tadalafil when used for treatment of pulmonary arterial HTN	Sildenafil or tadalafil when used for treatment of pulmonary arterial HTN
Sedatives/hypnotics	Triazolam; orally administered midazolam	Orally administered midazolam, triazolam

\*Studies of drug–drug interactions incomplete.

# Helpful Drug-Drug Interaction Resource

[www.hep-druginteractions.org](http://www.hep-druginteractions.org)

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### LATEST ARTICLES

**Reviews** - Nature Outlook, Hepatitis C supplement.

**Drug Interactions** - Telaprevir and ciclosporin or tacrolimus.

**Meeting Report** - 6th International Workshop on Hepatitis Clinical Pharmacology

**New Drugs** - Danoprevir and ritonavir

**Drug Interactions** - Studies with telaprevir and boceprevir.

**FDA News** - Telaprevir and Boceprevir

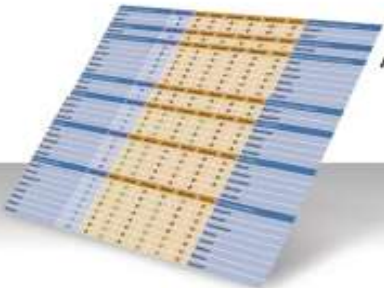
[Click here for previous news items](#)

### SITE UPDATES

**Boceprevir and Telaprevir**  
Boceprevir and telaprevir have been added as columns to the interaction charts. Where an interaction...

[>>more](#)


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### INTERACTIONS WITH TELAPREVIR AND BOCEPREVIR

#### Telaprevir & Boceprevir - INTERACTIONS NOW FULLY LISTED

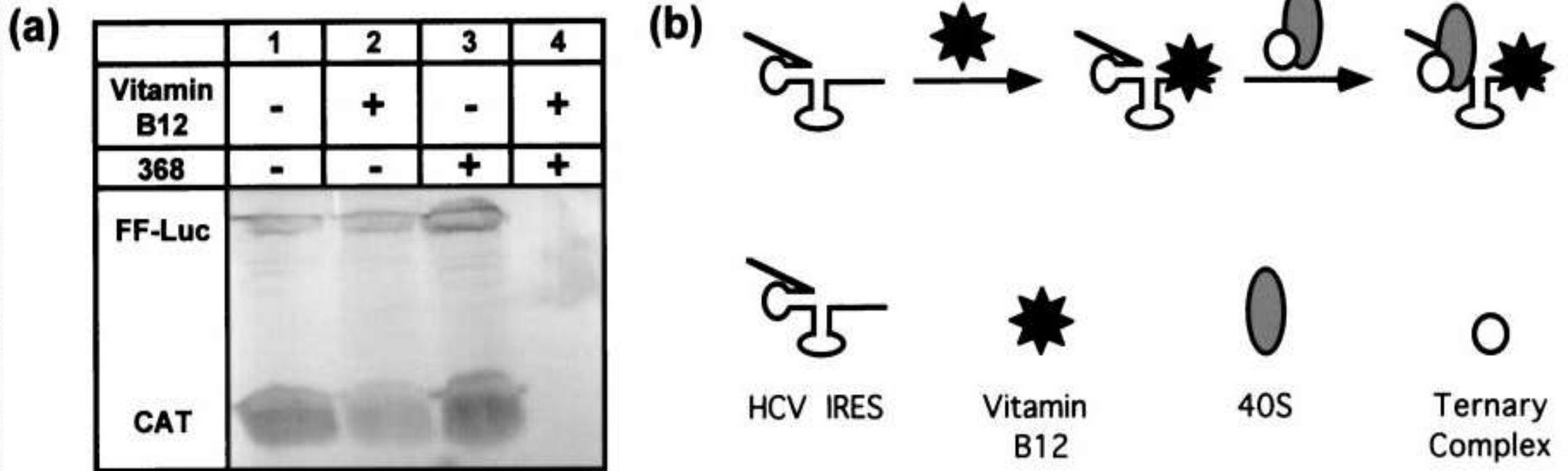
Telaprevir and boceprevir were licensed by the FDA in May and have been added as columns to the interaction charts. To view the interactions, click on the drug interaction chart section above.

# Vitamin B12

---

- MOA – interferes with the HCV IRES- dependent translation of viral protein
- Dose – Not yet established although the study used 5,000 IU given IM q month for duration of TX (24 wk or 48 wks)
- No additional side effect other than pIFN/RBV

# Vitamin B12 effect on HCV polyprotein translation



# Vitamin B12

Study enrolled 130 HCV mono-infected patients

---

Randomized into the 2 treatment arms –

SOC (pIFN/RBV) and SOC B12 (PIFN/RBV/B12)

Separate randomization were done for G2&3 and G1&4 to remove sampling bias

The groups were demographically matched. No AA were enrolled in the study

# Vitamin B12

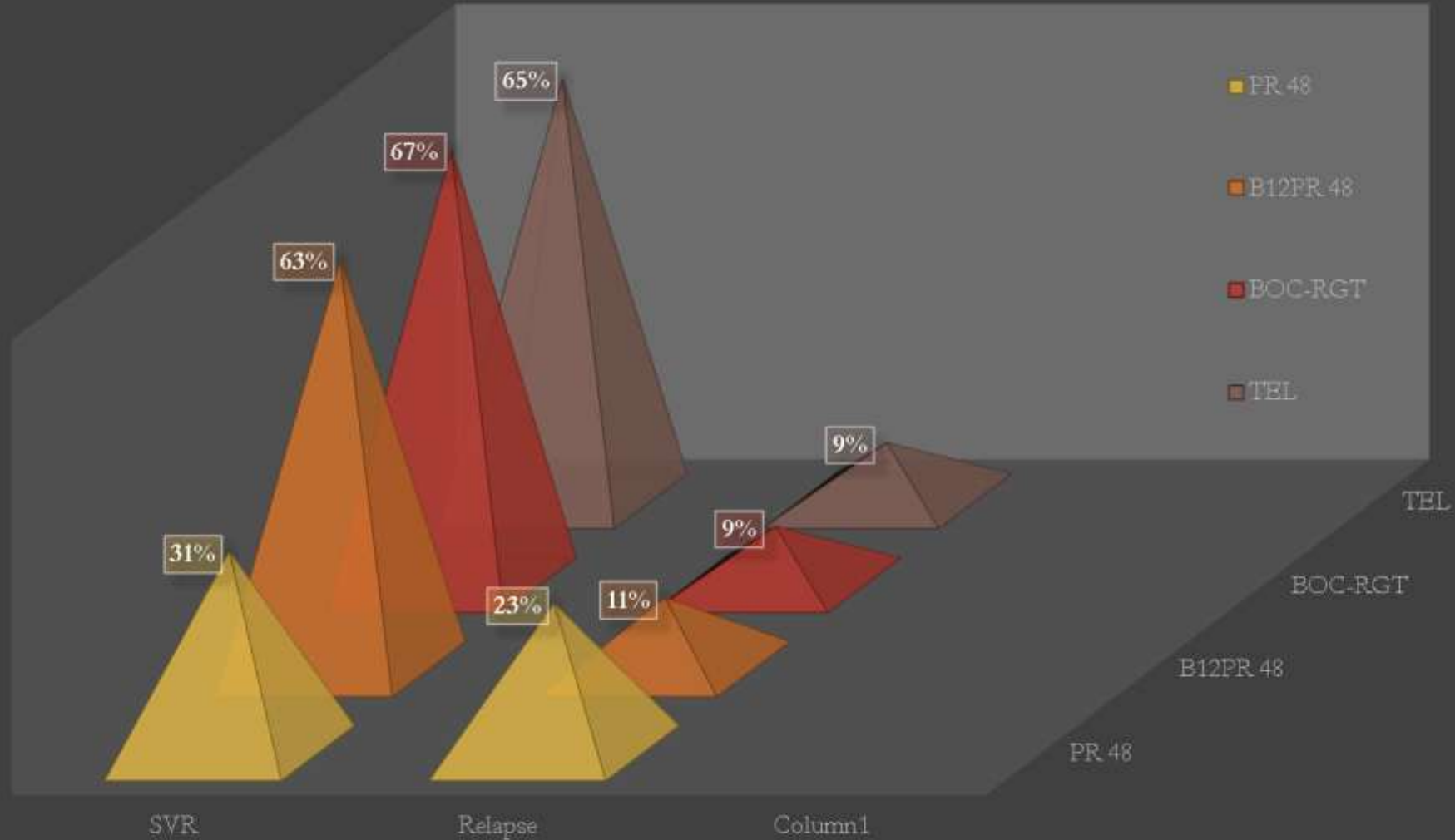
Results:

94 patients were available for analysis evenly randomized to the 2 treatment arms

---

Variables	SOC (%)	SOC B12 (%)	P value
SVR	38	72	.001
Genotype 1	22	63	.002
Genotype 2&3	73	93	NS

# Comparison of DAA's for G1 Treatment Naïve Patients



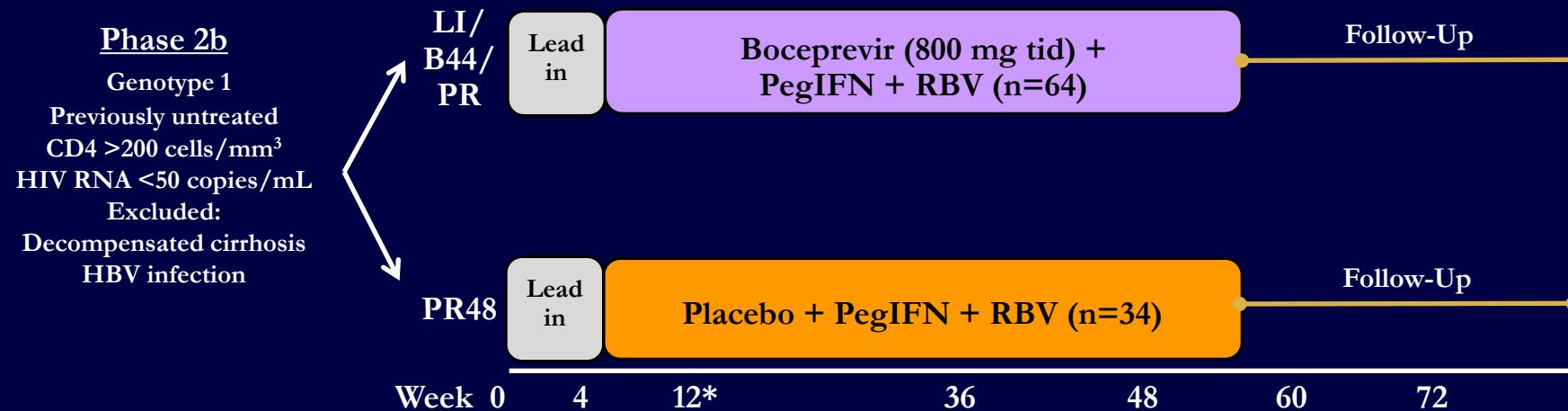
# Treatment Options

- PIFN/RBV/B12 x 24 weeks (G2,3), x 48 weeks (G1,4, all genotypes for HIV +)
- 

## Genotype 1 ONLY

- PIFN/RBV x 4 weeks then add BOC x 24 weeks – **STOP for RVR**
- PIFN/RBV x 4 weeks then add BOC x 24 weeks then PIFN/RBV x 20 weeks
- PIFN/RBV/TEL x 12 weeks then PIFN/RBV x 12 weeks – **STOP for RVR**
- PIFN/RBV/TEL x 12 weeks then PIFN/RBV x 36 weeks

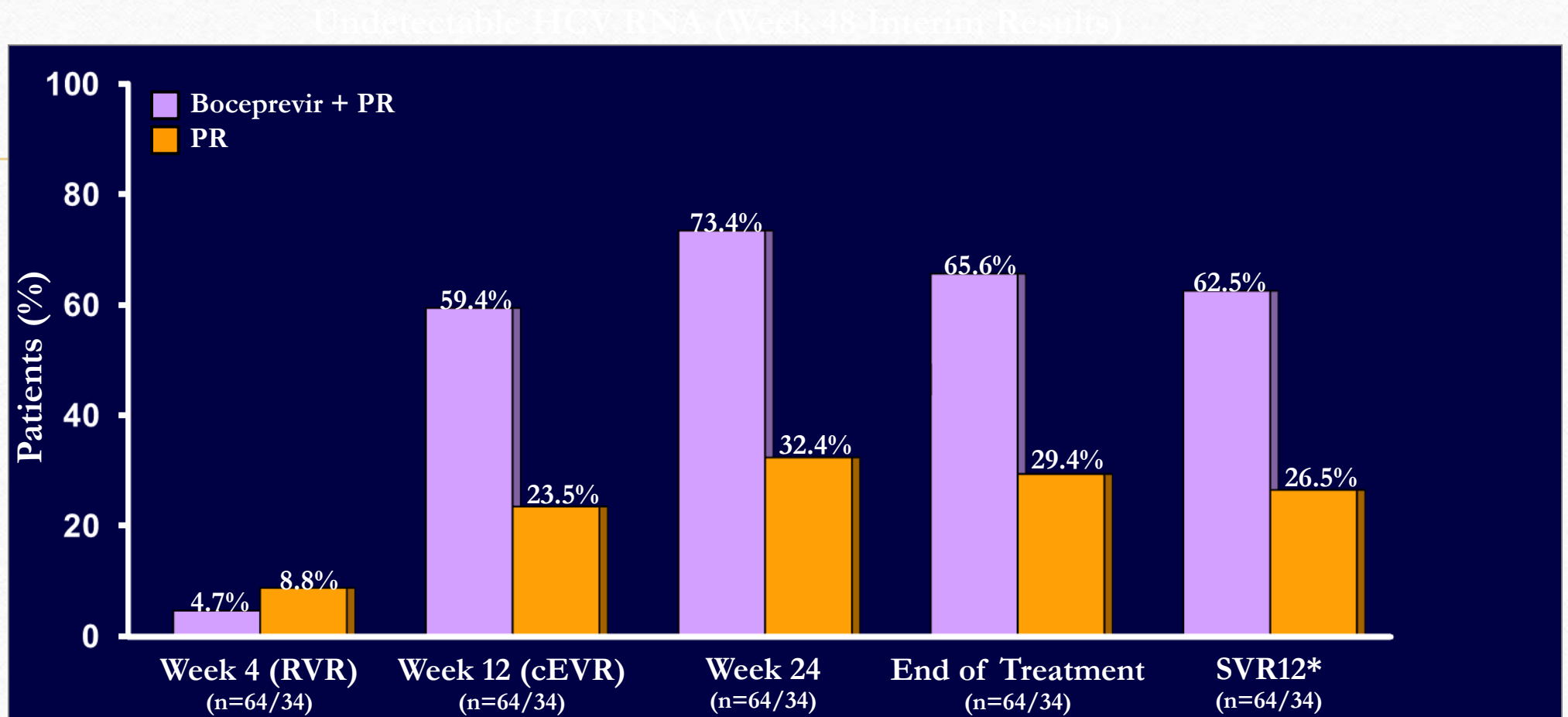
# Boceprevir-Based HCV Therapy in HCV/HIV Coinfection (48-Week Interim Analysis)



Weight-based ribavirin dosing (600-1400 mg bid).

\*Stopping rules: HCV RNA detectable at week 12.

# Boceprevir-Based HCV Therapy in HCV/HIV Coinfection



\*4 additional patients in boceprevir arm had SVR4 but had not reached SVR 12 and were not counted in the total percentage of SVR12 outcomes.

# Boceprevir-Based HCV Therapy in HCV/HIV Coinfection: Week 48 Safety

- Boceprevir arm had fewer HIV breakthroughs
  - 4.7% versus 11.7%
- Preliminary safety data consistent with HCV mono-infected patients
- Boceprevir arm
  - 27% of neutropenia cases were grade 3/4
  - 5% of anemia cases were grade 3/4

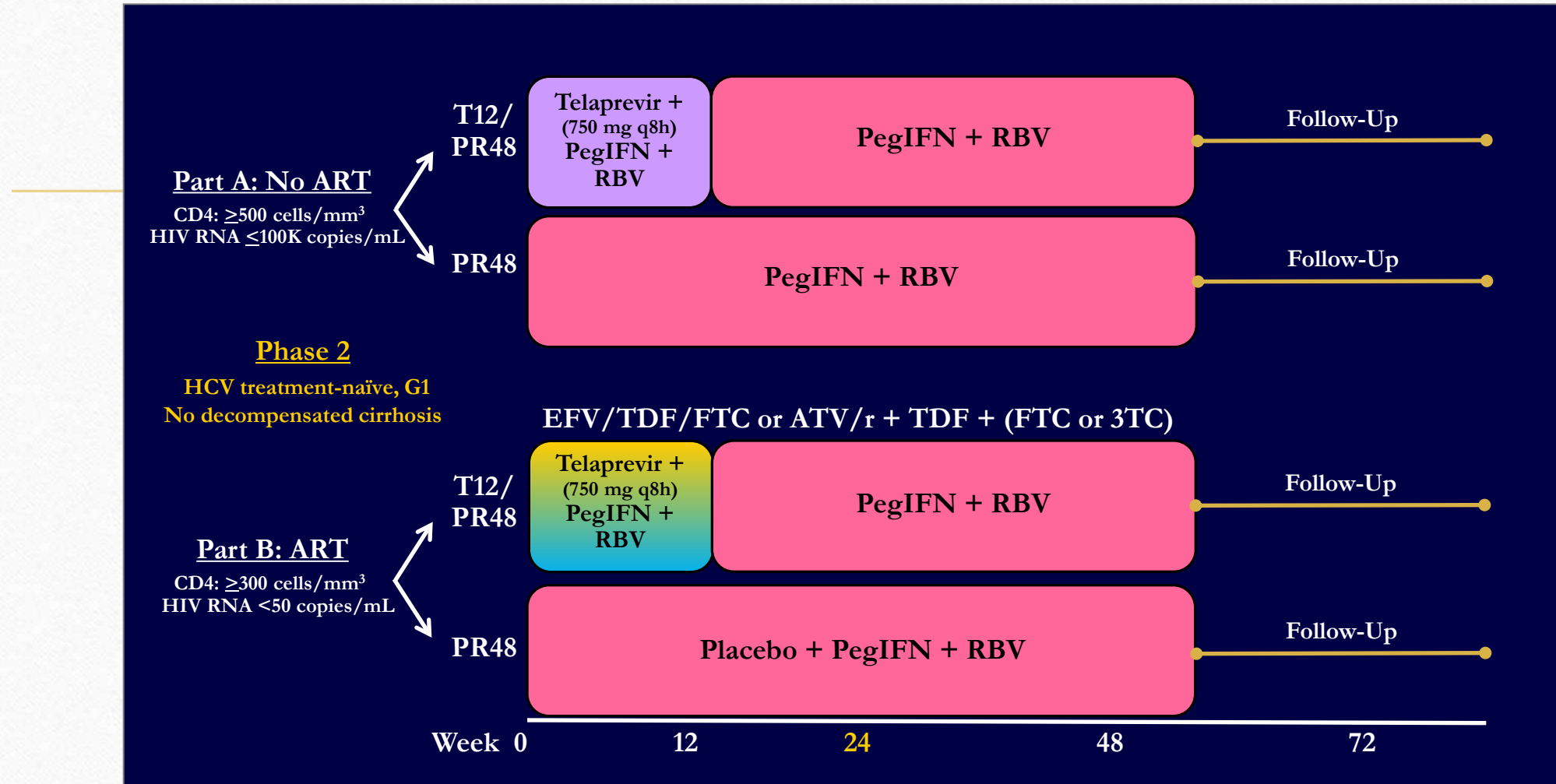
	Adverse Events (%)	
	Boceprevir/PR (n=64)	PR (n=34)
Anemia	41	26
Neutropenia	19	6
Pyrexia	36	21
Asthenia	34	24
Decreased appetite	34	18
Diarrhea	28	18
Dysgeusia	28	15
Vomiting	28	15
Flu-like illness	19	38

# Boceprevir Drug Interactions With ART

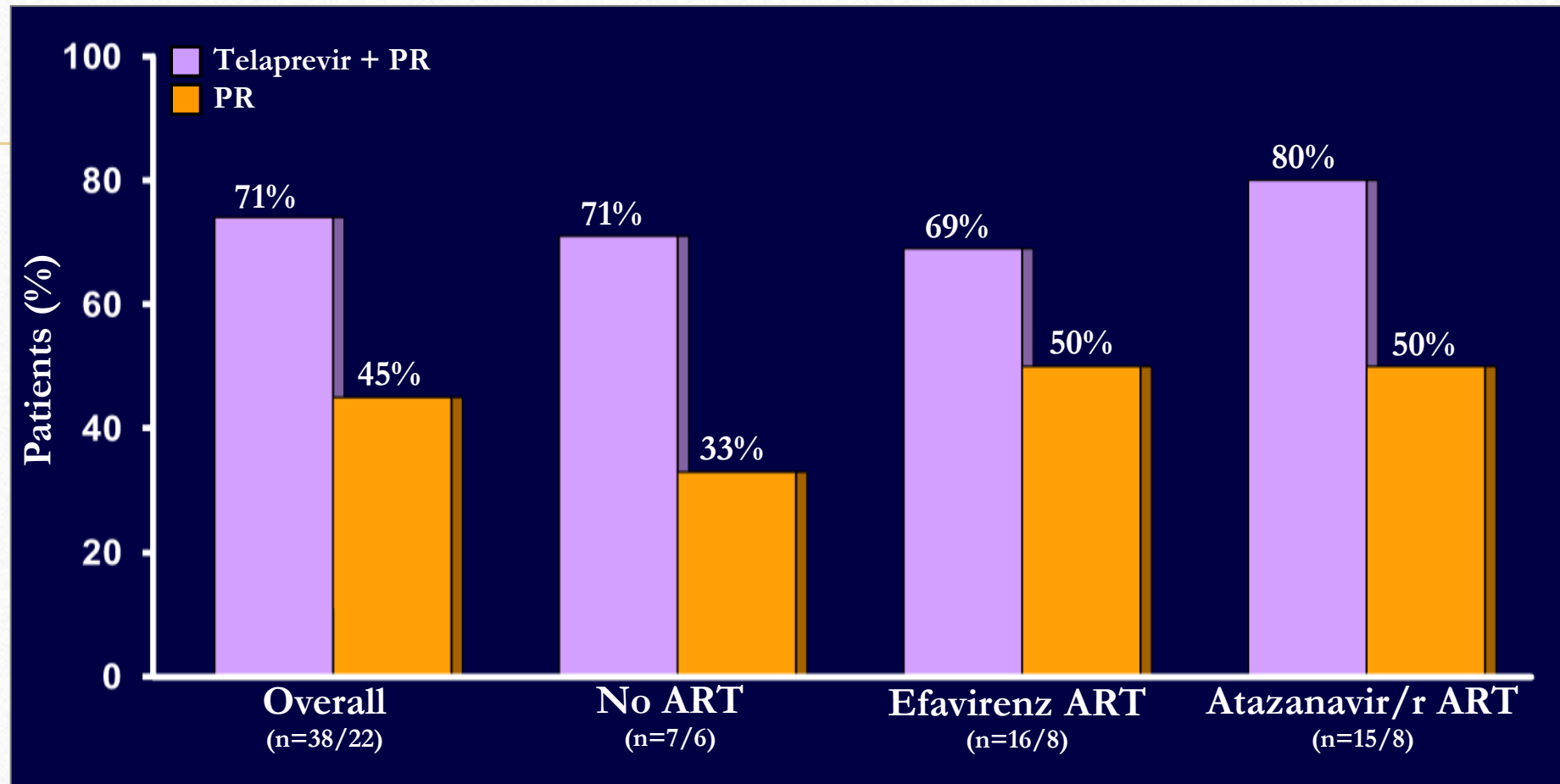
- Atazanavir/r, darunavir/r, lopinavir/r
  - Decrease in HIV PI trough concentrations (43%-59%)
  - Decrease boceprevir exposure with lopinavir/r and darunavir/r
- Efavirenz
  - Decrease boceprevir plasma trough concentrations
  - Avoid combination
- No drug interaction with raltegravir
- Ritonavir
  - Decrease boceprevir

Data are derived from healthy volunteers. No excess HIV viral breakthrough was observed in the phase 2 trials, suggesting effective drug levels were maintained, that pegIFN has provided new HIV antiviral coverage or some combination of both factors.

# Telaprevir-Based HCV Therapy in HCV/HIV Coinfection (24-Week Interim Analysis)



# Telaprevir-Based HCV Therapy in HCV/HIV Coinfection: SVR12



No HIV RNA breakthroughs.

Telaprevir-arm HCV RNA breakthrough: EFV/TDF/FTC (n=2); ATV/r + TDF/FTC (n=1).

## Telaprevir-Based HCV Therapy in HCV/HIV Coinfection: Week 24 Safety

- Telaprevir arm had a lower HCV relapse rate
  - 3% versus 15%
- Preliminary safety data consistent with HCV mono-infected patients
- Telaprevir arm
  - 0% severe rash
  - 29% of anemia cases were grade 3/4

	Adverse Events (%)	
	Telaprevir/PR (n=38)	PR (n=22)
Anemia	18	18
Neutropenia	19	6
Pruritus	39	9
Headache	37	27
Nausea	34	23
Fever	21	9
Depression	21	9

# Telaprevir Drug Interactions With ART

- Co-administration not recommended
  - Ritonavir-boosted darunavir, fosamprenavir, lopinavir

---

    - Decrease in telaprevir and darunavir, fosamprenavir; no change in lopinavir concentrations
- Atazanavir/ritonavir
  - Decrease telaprevir and increase in atazanavir concentrations
- Tenofovir DF
  - No change in telaprevir, increase in tenofovir DF
  - Discontinue tenofovir DF if toxicities develop

# Provisional Guidance: HCV PIs for Treatment of HCV in HIV-Infected

- When possible, HIV infection should be controlled before treatment with HCV PIs and pegIFN + RBV
  - Off ART: CD4 >500 cells/mm<sup>3</sup> and HIV RNA <20,000 copies/mL
  - On ART: HIV RNA <50 copies/mL
- Do not use HCV PIs with some medications that have proven or suspected pharmacologic interactions
  - Dosing adjustments may be required with other combinations
- Before using HCV Ps in any patient
  - Consult the full prescribing information for specific HCV PIs for a list of contraindicated drug combinations and details of multiple other drug-drug interactions

## Provisional Guidance: HCV PIs for Treatment of HCV in HIV-Infected

- PegIFN + RBV remain the standard of care
  - HCV genotype 2, 3, or 4
  - Pharmacokinetic interactions can not be mitigated
- For some coinfecting patients with chronic genotype 1 HCV infection, HCV PIs should be used with pegIFN + RBV
  - Do not use HCV PIs alone (or with pegIFN without RBV) because HCV PI-resistant viruses are rapidly selected
    - Contraindications to pegIFN + RBV preclude HCV PI use
- Liver failure (decompensated cirrhosis)
  - Do not use HCV PIs and/or pegIFN + RBV
- Significant fibrosis
  - Benefits of HCV PIs plus pegIFN + RBV are most likely to outweigh the risks
  - Some experts believe it is safer to monitor for evidence of progression until more data are available

## Antivirals with Proven Clinical Efficacy or Potentially Active in Chronic HCV Infection

### Direct Acting Agents

NS3-4A	NS5A	NS5B (nucleoside)	NS5B (non-nucleoside)
Telaprevir	Daclatasvir (BMS-790052)	Sofosbuvir (GS-7977)	Tegobuvir (GS-9190)
Boceprevir	ABT-267	Mericitabine (RG-7128)	Filibuvir (PF-868554)
Simeprevir (TMC435)	PPI-461	IDX-184	Setrobuvir (ANA598)
Faldeprevir (BI201335)	GS-5885	GS-938	BI207127
Danoprevir /r (RG-7227)	GSK-2336805	GS-6620	VX-222
Vaniprevir (MK-7009)	ACH-2928	TMC-649128	ABT-072
Asunaprevir (BMS-650032)	ACH-3102		ABT-333
GS-9256			BMS-791325
GS-9451			TMC-647055
ABT-450 /r			VCH-759
Sovaprevir (ACH-1625)			GS-9669
MK-5172			

### Host-Targeting

Alisporivir (DEB025, cyclophilin)	SCY-465 (cyclophilin)	ANA-773 (TLR-7)
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# HCV – the disease in HIV infected Adult

## The Barriers to Care

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1. Lack of knowledge of infection
2. Limited number of providers capable and willing to treat HCV
3. Psychosocial barriers that prevent successful evaluation and treatment
4. Significant cost of current HCV regimens
5. Interferon based regimens, when used, were riddled with side effects and, until recently, were often not successful.

# HCV – the disease in HIV infected Adult

## Measures to Overcome the Barriers

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1. Education focused at preventing newly acquired HCV
2. Increasing provider awareness and training in screening, counseling and treating patients coinfectd with HIV and HCV
3. More aggressive approach to controlling medical and psychiatric comorbidity; early initiation of ART for ALL coinfectd patients, regardless of CD4 count as this has been shown to slow progression of liver fibrosis.
4. Improve safety, tolerability and efficacy of treatment options for HCV.

# THANK YOUs

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- Virology Team at UTMB-CMC
- Dr Olawutoyin Adyemi